JANUARY 1978 • VOL. 187, NO. 1
ISSN 0003-4932 ANSUA5

Acc
27.4.78

CUK-H01404-19-P024762

ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice

Since 1885

19

J. B. LIPPINCOTT COMPANY
PHILADELPHIA • TORONTO

ERSITY COLLE OF MEDICI
LIBRARY

The Dilaudid Difference.

The one oral narcotic analgesic with all these features:

Dilaudid provides dosage flexibility: 1 mg, 2 mg, 3 mg, 4 mg
4 dosage strengths to meet the wide range of individual patient tolerances

---

Dilaudid keeps nausea, vomiting and drowsiness to a minimum

Dilaudid provides significant pain relief within 30 minutes and pain is often controlled for more than five hours.*

Dilaudid allows most patients to remain physically active and alert

---

Dilaudid is color coded
Easy identification
Easy patient handling

Dilaudid is a single entity drug

---

*Data on file, Medical Department, Knoll Pharmaceutical Co.

P 24,762

Oral Dilaudid®
hydromorphone HCl ⒸII

For the moderate to severe short-term pain you see every day.

Description: Dilaudid is hydromorphone, a hydrogenated ketone of morphine.
Indications: For relief of moderate to severe pain.
Contraindications: Suspected increased intracranial pressure; status asthmaticus.
Warnings: May be habit forming with a potential for addiction equivalent to morphine in equi-analgesic doses. Tolerance may also occur. As with all narcotics, use in early pregnancy only when expected benefits outweigh risks.
Adverse Effects: Nausea, vomiting, diarrhea, constipation, anorexia and somnolence may occur although unlikely with appropriate dose selection.
Dosage and Administration: Dosage must be individualized. The usual adult dose is 2 mg every 4-6 hours, as necessary, for moderate to moderately severe pain. For more severe pain, 3-4 mg or more every 4-6 hours, as necessary, may be required.
Treatment of Overdosage: If overdosage is treated within an hour, emesis and gastric lavage should be attempted. Special attention should be given to respiration and, if depression occurs, it may be antagonized by the use of naloxone hydrochloride (Narcan®)—Endo, nalorphine hydrochloride (Nalline®)—Merck, Sharp & Dohme or levallorphan tartrate (Lorfan®)—Roche, as recommended by the manufacturer. Other supportive measures should be applied when indicated.
How Supplied: Dilaudid HCl color coded tablets (NOT FOR INJECTION) imprinted with K logo on one side and potency on other side as follows: green—1 mg; orange—2 mg; pink—3 mg and yellow—4 mg. Available in: 1 mg—bottles of 100 (NDC #0044-1021-02), 2 mg—bottles of 100 (NDC #0044-1022-02) and 500 (NDC #0044-1022-03), 3 mg—bottles of 100 (NDC #0044-1023-02), 4 mg—bottles of 100 (NDC #0044-1024-02) and 500 (NDC #0044-1024-03).

Knoll Pharmaceutical Company
Whippany, New Jersey 07981

Member Company, Certified Medical Representatives Institute, Inc.

Beaver

MINI-BLADES®

THESE are the blades designed specifically for fine surgical procedures. We show just four shapes but we have many more. In fact, we have some very special designs for the fussiest procedures. Try them — you'll like them!

NOW...
In Autoclavable Foil Packages.

Write for more information or Call Free 1-800-225-1482

RUDOLPH Beaver INC. ***SURGICAL PRODUCTS***

480 TRAPELO ROAD • BELMONT, MASS. 02178

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

DAVID C. SABISTON, JR., M.D., *Chairman*
Durham, N. C.

J. WESLEY ALEXANDER, M.D.
Cincinnati, O.

WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.

W. GERALD AUSTEN, M.D.
Boston, Mass.

HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.

WARREN H. COLE, M.D.
Asheville, N. C.

MICHAEL E. DE BAKEY, M.D.
Houston, Tex.

STANELY J. DUDRICK, M.D.
Houston, Tex.

J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.

PAUL A. EBERT, M.D.
San Francisco, Calif.

ERIC W. FONKALSRUD, M.D.
Los Angeles, Calif.

FRANK L. A. GERBODE, M.D.
San Francisco, Calif.

FRANK GLENN, M.D.
New York, N. Y.

FRASER N. GURD, M.D.
Ottawa, Canada

OLGA M. JONASSON, M.D.
Chicago, Ill.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.

LEONARD D. MILLER, M.D.
Philadelphia, Pa.

FRANCIS D. MOORE, M.D.
Boston, Mass.

WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.

JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.

JONATHAN E. RHOADS, M.D.
Philadelphia, Pa.

PAUL S. RUSSELL, M.D.
Boston, Mass.

JOHN A. SCHILLING, M.D.
Seattle, Wash.

G. THOMAS SHIRES, M.D.
New York, N. Y.

HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.

DAVID B. SKINNER, M.D.
Chicago, Ill.

FRANK C. SPENCER, M.D.
New York, N. Y.

SAMUEL A. WELLS, JR., M.D.
Durham, N. C.

Emeritus Members

Brian B. Blades, M.D., Washington, D.C., William F. Rienhoff, Jr., Baltimore, Md.
John D. Stewart, M.D., Boca Raton, Fla.

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Second-class postage paid at Philadelphia, Pa., and at additional mailing offices. Published monthly.
Subscription $26.00 per United States. Resident Rate (U.S. only) $19.00.
All other countries $35.00. Single issue $4.00. All prices include postage.

Copyright © 1978 by J. B. Lippincott Co., East Washington Square, Philadelphia, Pa. 19105. Printed in U.S.A.

ANTISEPTIC SECURITY

in scrubbing and prepping

For surgeons, nurses and patients the prompt, broad-spectrum action of BETADINE Microbicides provides topical antiseptic security.

BETADINE Surgical Scrub, for scrubbing by the surgical team and for optimal skin degerming in prepping the patient . . . promptly achieves full microbicidal effect with each usage . . . (in the rare instance of local irritation or sensitivity, discontinue use in the individual).

BETADINE Solution or BETADINE Aerosol Spray, to enhance antisepsis in prepping after initial use of BETADINE Surgical Scrub. BETADINE Solution and BETADINE Aerosol Spray are film-forming . . . active in the presence of blood, pus and serum . . . help maintain postoperative antisepsis when applied to incisions.

Purdue Frederick

©COPYRIGHT 1975, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A7982 165175

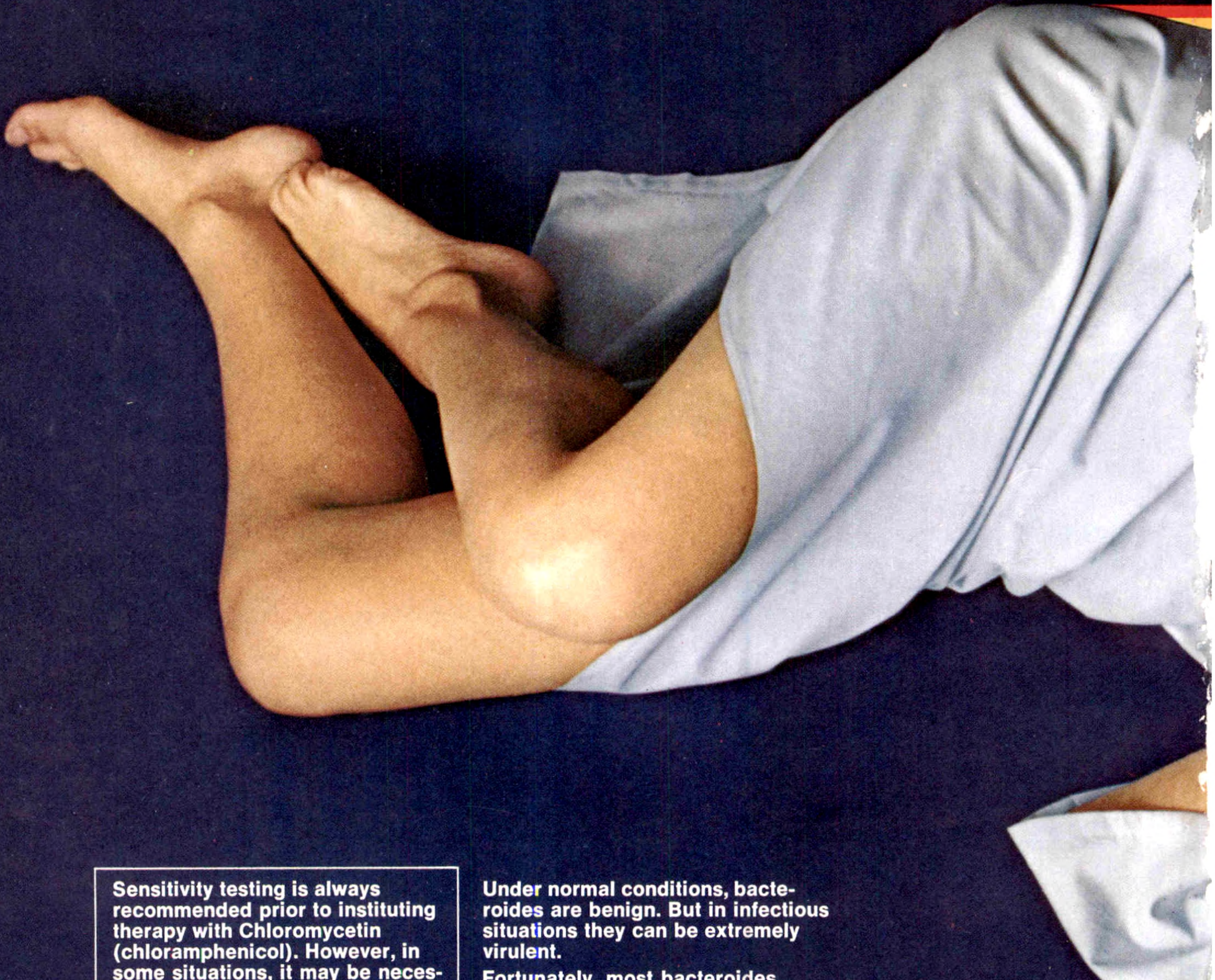
BETADINE®
Microbicides

Foremost documented
broad-spectrum
topical microbicides

Bacteroides

may be implicated
in a number of clinical situations,
including . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena



Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated.

But when bacteroides are implicated, Chloromycetin (chloramphenicol) therapy may well be the conservative course. For, in such situations, the benefits-to-risk ratio with Chloromycetin is very favorable.

See next page for full prescribing information.

Bacteroides...

often an indication for

CHLOROMYCETIN®

(chloramphenicol) Sodium Succinate

PARKE-DAVIS

Prescribing information—Chloromycetin (chloramphenicol) Sodium Succinate
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**
   It is not recommended for the routine treatment of the typhoid carrier state.
2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.
   a) *Salmonella* species
   b) *H influenzae,* specifically meningeal infections
   c) Rickettsia
   d) Lymphogranuloma-psittacosis group
   e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.
2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.
4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.
5. There are no studies to establish the safety of this drug in pregnancy.
6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).
7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.
8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
  - (1) abdominal distension with or without emesis;
  - (2) progressive pallid cyanosis;
  - (3) vasomotor collapse, frequently accompanied by irregular respiration;
  - (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants
(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off

RJ

PD-JA-1280-2-P (2-75)

PARKE, DAVIS & COMPANY Detroit, Michigan 48232

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

ANNALS OF SURGERY

Vol. 187 January 1978 No. 1

CONTENTS

1 **Neonatal Necrotizing Enterocolitis: Therapeutic Decisions Based Upon Clinical Staging**
Martin J. Bell, M.D., *Jessie L. Ternberg,* M.D., *Ralph D. Feigin,* M.D., *James P. Keating,* M.D., *Richard Marshall,* M.D., *Leslie Barton,* M.D., *Thomas Brotherton,* M.S., *St. Louis, Missouri*

8 **Multiple Carcinomas of the Large Bowel: A Natural Experiment in Etiology and Pathogenesis**
Warren E. Enker, M.D., *Slobodan Dragacevic,* M.D., *Chicago, Illinois*

12 **Reserpine Treatment of Raynaud's Disease**
Birgitta Arneklo Nobin, M.D., *Steen Levin Nielsen,* M.D., *Bo Eklov,* M.D., *Niels A. Lassen,* M.D., *Copenhagen, Denmark*

17 **Frozen Section Diagnosis of Breast Lesions: Recent Experience with 556 Consecutive Biopsies**
Paul Peter Rosen, M.D., *New York, New York*

20 **Endoscopic Retrograde Cholangiography (ERC) in Surgical Emergencies**
L. Safrany, N. Van Husen, G. Kautz, G. Wittrin, M. Clemens, R. Weitemeyer, Hamilton, Canada

24 **Splenectomy in Myeloid Metaplasia**
E. B. Cabot, M.D., *M. F. Brennan,* M.D., *D. S. Rosenthal,* M.D., *R. E. Wilson,* M.D.

31 **Albumin Uptake by Skin, Skeletal Muscle and Lung in Living and Dying Patients**
Paul C. Smith, M.B., *Howard A. Frank,* M.D., *Earl J. Kasdon,* M.D., *Elizabeth C. Dearborn,* B.S., *John J. Skillman,* M.D., *Boston, Massachusetts*

38 **Dearterialization of the Liver for Metastatic Cancer: Clinical, Angiographic and Pathologic Observations**
William V. McDermott, Jr., M.D., *Allen L. Paris,* M.D., *Melvin E. Clouse,* M.D., *William A. Meissner,* M.D., *Boston, Massachusetts*

47 **A "New" Diaphragm Following Prosthetic Repair of Experimental Hemidiaphragmatic Defects in the Pup**
Robert J. Touloukian, M.D., *New Haven, Connecticut*

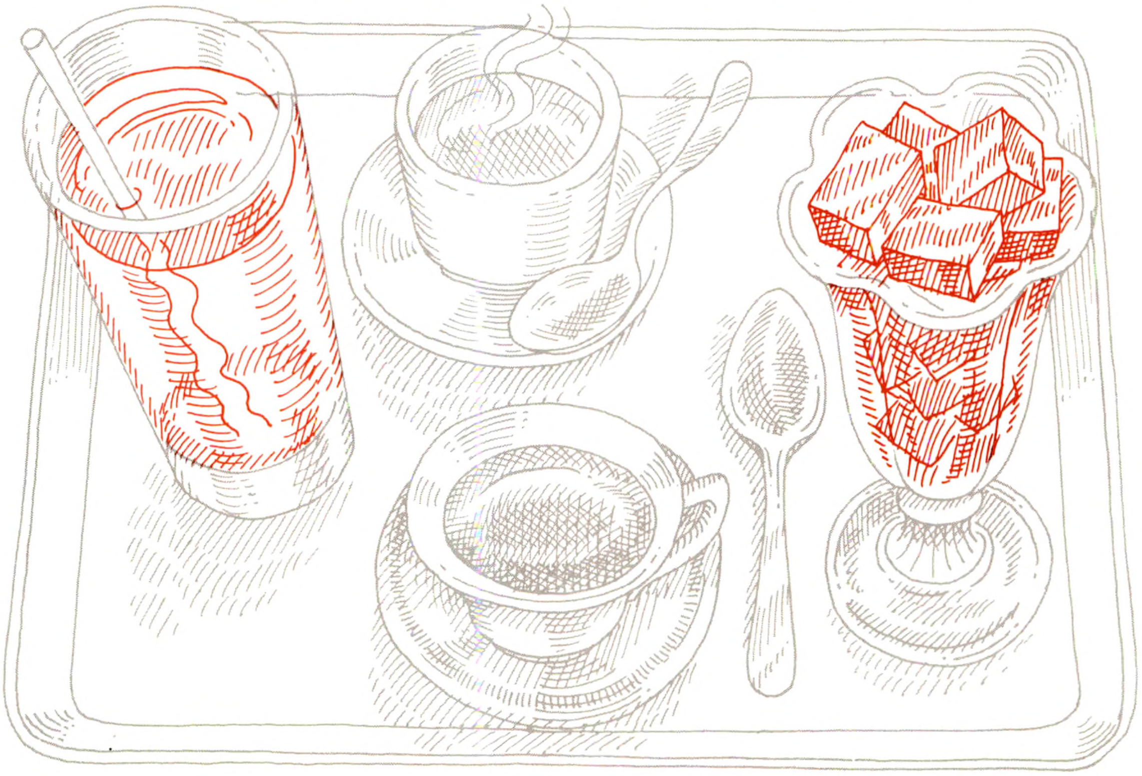
52 **The Role of Splenectomy in the Treatment of Thrombocytopenic Purpura Due to Systemic Lupus Erythematosus**
William P. Homan, M.D., *Peter Dineen,* M.D., *New York, New York*

Starvation diet?

Standard clear liquid regimen: 400 kcal daily—trace protein

Not when you fortify with **Vivonex® HN!**

Clear liquid regimen fortified with 5 packets Vivonex HN:
1,900 kcal, 10 gm nitrogen (62.5 gm protein) daily

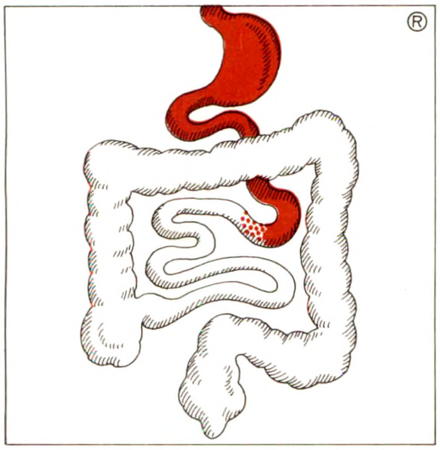


For the nutritional management of protein-calorie malnutrition...Vivonex HN

The usual clear liquid regimen provides only 400 calories daily, with only trace protein. The addition of Vivonex HN to the regimen can add substantial amounts of vital protein and calories for the nutritional management of protein-calorie malnutrition. Vivonex HN is readily accepted by patients on clear liquid regimens when mixed into gelatin desserts, or when served as a beverage in the various flavors now available with Vivonex Flavor Packets.

Because Vivonex HN is formulated with free amino acids, simple carbohydrate and low fat, it requires virtually no active digestion and is absorbed almost completely with negligible residue. Thus it supports the diet objective.

Add Vivonex HN to conventional clear liquids before and after surgery, and when clean-bowel preparation is necessary before surgery or diagnostic procedures. Vivonex HN is also valuable as an enteral alternative to parenteral feeding, as an adjunct to routine parenteral glucose and fluids, and for patients with GI disorders.



Protein-calorie fortification... negligible residue

Vivonex® HN HIGH NITROGEN SOLUBLE POWDER

free amino acid...complete enteral nutrition
minimal digestion...maximal absorption

Supplied unflavored in boxes containing ten 80-gram packets. Each packet provides 300 kcal, 2 gm usable nitrogen (12.5 gm usable protein), as well as carbohydrate, fat, essential vitamins and minerals.

Flavor with Vivonex Flavor Packets
(artificially flavored) Orange, strawberry, grape, beef broth, and tomato. *Also available:* Vivonex Standard Diet. Supplied unflavored in boxes containing six 80-gram packets. Each packet provides 300 kcal. Six packets provide 1,800 kcal, 5.88 gm usable nitrogen (36.75 gm usable protein).

Please note: Information on Vivonex usage and precautions accompanies the product and should be reviewed before use.

® Originators of chemically defined diets
EATON LABORATORIES
division of Morton-Norwich Products, Inc.
Norwich, New York 13815

CONTENTS *Continued*

57 **The Effect of Jejunoileal Bypass on Bile Composition and the Formation of Biliary Calculi**
Leslie Wise, M.D., *Theodore Stein,* M.S., *St. Louis, Missouri*

63 **A Density Test for the Intraoperative Differentiation of Parathyroid Hyperplasia from Neoplasia**
Chiu-An Wang, M.D., *Sidney V. Rieder,* PH.D., *Boston, Massachusetts*

68 **Does Adrenergic Activity Suppress Insulin Secretion During Surgery? A Clinical Experiment with Halothane Anesthesia**
Markku Aarimaa, M.D., *Erkka Syvalahti,* M.D., *Jari Ovaska,* M.B., *Turku, Finland*

73 **Hemodynamic Effects of Prolonged Hyperoxia**
Jon F. Moran, M.D., *Walter G. Wolfe,* M.D., *Durham, North Carolina*

79 **Autotransplantation of Pancreatic Fragments to the Portal Vein and Spleen of Totally Pancreatectomized Dogs: A Comparative Evaluation**
George J. Kretschmer, M.D., *David E. R. Sutherland,* M.D., *Arthur J. Matas,* M.D., *William D. Payne,* M.D., *John S. Najarian,* M.D., *Minneapolis, Minnesota*

87 **Human Parathyroid Cryopreservation: In Vitro Testing of Function by Parathyroid Hormone Release**
Murray F. Brennan, M.D., *Edward M. Brown,* M.D., *Henry F. Sears,* M.D., *Gerald D. Aurbach,* M.D., *Bethesda, Maryland*

91 **Control of Gastric Emptying: Interaction of the Vagus and Pyloric Antrum**
T. Yamagishi, M.D., *H. T. Debas,* M.D., *Vancouver, B.C., Canada*

95 **Studies in Pharmacokinetics and Tolerance of Substances Temporarily Retained in the Liver by Microsphere Embolization**
Bo Lindell, M.D., *Karl Fredrik Aronsen,* M.D., *Bertil Nosslin,* M.D., *Ulf Rothman,* M.D., *Malmo, Sweden*

100 **Techniques in Surgery: The Clinical Use of the Naso-gastric Duodenal Mercury Tip Sump Tube in Abdominal Surgery and in the Management of Intestinal Obstruction**
Joseph Hodge, M.D., *Spartanburg, South Carolina*

- **Compact...**easy to store...all in a sealed, plastic container
- **Versatile...**easily snaps onto the top of a magnesium citrate bottle...can be used with other saline cathartics or with castor oil
- **Economical...**suggested retail price is less than most other kits
- **Convenient...**for nursing staff or the outpatient. Sold in a handy dispenser of 5.

With the Dulcolax Bowel Prep Kit plus magnesium citrate "...the reexamination rate of patients because of poorly cleansed colons has fallen to approximately 1 percent of all barium enema studies."[1]

[1] Sorrentino A P et al. Am J Hosp Pharm *26*:432-435, 1969.

Boehringer Ingelheim Ltd.
Ridgefield, CT 06877

Each kit contains:

4 Dulcolax tablets of 5 mg bisacodyl

complete patient instructions

1 Dulcolax suppository of 10 mg bisacodyl

Announcing the New Dulcolax® Bowel Prep Kit

When conservative measures won't stop bleeding...

suspect hyperfibrinolysis...

Consider AMICAR® to bring on hemostasis

Stat Therapy For Hemostatic Results
■ inhibits the process that causes clot dissolution ■ prevents excessive breakdown of fibrin and fibrinogen ■ hemorrhage stops because a hemostatic plug can form ■ available in 3 forms that follow need – I.V. (250 mg./ml.), Tablets of 500 mg., Syrup (250 mg./ml.) ■ compatible with infusions of whole blood, fibrin and other measures when required in conjunction with AMICAR.

AMICAR®
Aminocaproic Acid

control in
hyperfibrinolytic
bleeding

Please see following page for prescribing information.

INDICATIONS: AMICAR has proved useful, in many instances, in the treatment of excessive bleeding which results from *systemic hyperfibrinolysis* and *urinary fibrinolysis*. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Systemic hyperfibrinolysis, a pathological condition, may frequently be associated with *surgical complications* following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; *hematological disorders* such as aplastic anemia, *abruptio placentae, hepatic cirrhosis, neoplastic disease* such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is *surgical hematuria* (following prostatectomy and nephrectomy) or *non-surgical hematuria* (accompanying polycystic or neoplastic diseases of the genitourinary system).

CONTRAINDICATIONS: AMICAR should not be used when there is evidence of an active intravascular clotting process.

WARNINGS: Safe use of AMICAR has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of child-bearing potential and particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible hazards.

PRECAUTIONS: AMICAR *aminocaproic acid* has a very specific action in that it inhibits both plasminogen activator substances and, to a lesser degree, plasmin activity. The drug should NOT be administered without a definite diagnosis, and/or laboratory findings indicative of hyperfibrinolysis (hyperplasminemia).*

*Stefanini, M. and Dameshek, W.: The Hemorrhagic Disorders, Ed. 2, New York, Grune and Stratton, pp. 510-514, 1962.

The use of AMICAR should be accompanied by tests designed to determine the amount of fibrinolysis present. There are presently available (a) general tests, such as those for the determination of the lysis of a clot of blood or plasma and (b) more specific tests for the study of various phases of fibrinolytic mechanisms. These latter tests include both semiquantitative and quantitative technics for the determination of profibrinolysin, fibrinolysin, and antifibrinolysin.

Animal experiments indicate particular caution should be taken in administering AMICAR to patients with cardiac, hepatic or renal diseases.

Demonstrable animal pathology in some cases have shown endocardial hemorrhages and myocardial fat degeneration. The use of this drug should thus be restricted to patients in whom the benefit hoped for would outweigh the hazard. Physicians are cautioned in the use of this product because of animal data showing rat teratogenicity and kidney concretions.

Rapid intravenous administration of the drug should be avoided since this may induce hypotension, bradycardia and/or arrhythmia.

One case of *cardiac* and *hepatic lesions* observed in man has been reported. The patient received 2 grams of aminocaproic acid every 6 hours for a total dose of 26 grams. Death was due to continued cerebral vascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

If it is accepted that fibrinolysis is a normal process, potentially active at all times to ensure the fluidity of blood, then it must also be accepted that inhibition of fibrinolysis by aminocaproic acid *may* result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of *intravascular clotting* which followed this treatment. Rather, it appears that such intravascular clotting was most likely a result of the fibrinolytic disease being treated.

It has been postulated that *extravascular clots* formed *in vivo* with incorporated aminocaproic acid may not undergo spontaneous lysis as do normal clots. However, it is the consensus of experts that the few reported cases of extravascular clotting could have occurred in the absence of aminocaproic acid treatment.

ADVERSE REACTIONS: Occasionally nausea, cramps, diarrhea, dizziness, tinnitus, malaise, conjunctival suffusion, nasal stuffiness, headache, and skin rash have been reported as results of the administration of aminocaproic acid. Only rarely has it been necessary to discontinue or reduce medication because of one or more of these effects.

Thrombophlebitis, a possibility with all intravenous therapy, should be guarded against by strict attention to the proper insertion of the needle and the fixing of its position.

DOSAGE AND ADMINISTRATION: *INITIAL THERAPY*—An initial priming dose of 5 grams of AMICAR administered either orally or intravenously followed by 1 to 1¼ gram doses at hourly intervals thereafter should achieve and sustain plasma levels of 0.130 mg./ml. of the drug. This is the concentration apparently necessary for the inhibition of systemic hyperfibrinolysis. Administration of more than 30 grams in any 24-hour period is not recommended.

INTRAVENOUS: AMICAR *aminocaproic acid* intravenous is administered by infusion, utilizing the usual compatible intravenous vehicles (e.g. Sterile Water for Injection, physiologic saline, 5% dextrose or Ringer's Solution). RAPID INJECTION OF AMICAR INTRAVENOUS UNDILUTED INTO A VEIN IS NOT RECOMMENDED.

For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 16 to 20 cc. (4 to 5 grams) of AMICAR intravenous be administered by infusion during the first hour of treatment, followed by a continuing infusion at the rate of 4 cc. (1.0 gram) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

ORAL THERAPY: If the patient is able to take medication by mouth, an identical dosage regimen may be followed by administering AMICAR Tablets or 25% Syrup as follows: For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 10 tablets (5 grams) or 4 teaspoonfuls of syrup (5 grams) of AMICAR be administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 gram) or 1 teaspoonful of syrup (1¼ grams) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

REV. 7/72

LEDERLE LABORATORIES

FACULTY POSITION OPEN

College of Medicine, King Faisal University
Dammam, Saudi Arabia

PROFESSOR AND CHAIRMAN,
DEPARTMENT OF SURGERY

Applications are invited from U.S., British and Canadian surgeons with at least ten years teaching experience in a medical school. Opening is for September 1978; interviews scheduled with the Dean in the United States early in 1978. Language of instruction is English.

Salary and Benefits:

Academic Salary monthly in Saudi Riyals (SR)	*+ Clinical Bonus of 50%*	*= Total approximate* *annually in* U.S. dollars
SR 10,000	SR 5,000	$50,000

Free furnished accommodations and annual leave with travel allowance to country of origin for family of four. No Saudi income tax.

Send curriculum and references with addresses and telephone numbers to:

Mohammed T. Altorki, M.D., MRCP
Dean of the Medical Faculty
King Faisal University
c/o Saudi Arabian Educational Mission
2223 West Loop South, Suite 400
Houston, Texas 77027

Specify dates of teaching appointments and availability.

CHANGE OF ADDRESS

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the *Journal*.

Send Change of Address cards to:

ANNALS OF SURGERY
c/o Fulfillment Manager
East Washington Square
Philadelphia, Penna. 19105

Smooth way to rough it.

Our natural-fiber, bulk-producing laxative is the easy way to give your patients the roughage they need. In constipation, whether simple or associated with such conditions as diverticular disease, irritable bowel syndrome or hemorrhoids, Metamucil leads to the soft life.

The powder mixes with water or juices; the Instant Mix is citrus-flavored. Deliciously easy to take.

Metamucil®
brand of
psyllium hydrophilic mucilloid

SEARLE Searle Laboratories
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

661

Complications in Vascular Surgery

***Edited by* HUGH G. BEEBE, M.D.,**
With 18 Contributors.

Outstanding vascular surgeons from all sections of the country have pooled their composite experience and knowledge for this in-depth work. Each has written on a specific vascular complication and gives you the benefit of his expertise in this area. Three objectives are always in view: 1) To help you prevent complications where the causes are known and can be anticipated. 2) To provide you with a clear guide to the management of complications. 3) To establish a foundation of information from which you can deal logically and effectively with problems not described. This work reaps the benefit of significant appraisals of long-term follow-up studies that became possible during the last ten years.

402 Pages • 175 Illustrations • 1973 • $28.00

J. B. LIPPINCOTT CO.
East Washington Square, Phila., Pa. 19105

Please send me:

Complications in Vascular Surgery $28.00

☐ Payment Enclosed (Save postage & handling) ☐ Charge and Bill me (Plus postage & handling)

Name ____________________

Address ____________________

____________________ Zip ________

AS 1/78

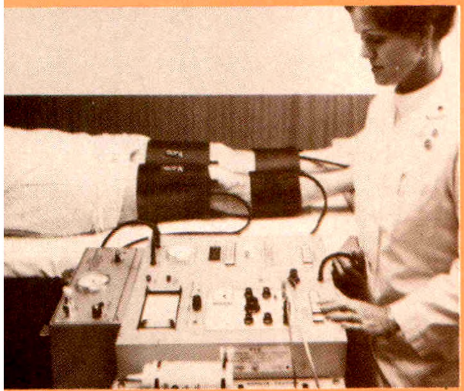
Lippincott

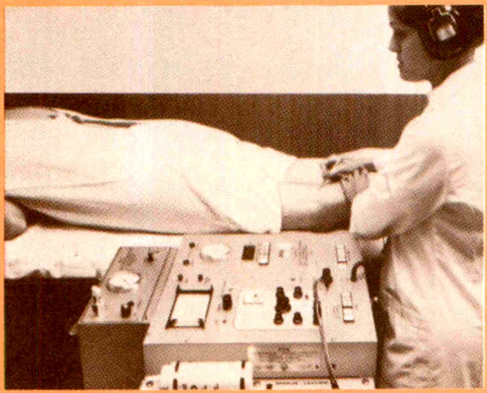
The LSI NON-INVASIVE Clinical Vascular Laboratory

PULSE VOLUME RECORDER (PVR®)*

An Extensively Documented Clinical Procedure
or the Quantitative Evaluation of Peripheral Vascular Disease:
Arterial—Venous—Cerebral Vascular

Arterial



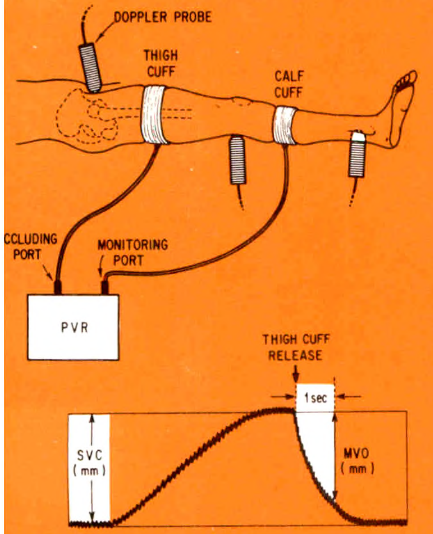


tal Segmental Perfusion (primary ssel plus collaterals) is accurately cumented at the thigh-calf-ankle-etatarsal level and digits.

The built-in Doppler facilitates the measurement of pressures along the arterial tree.

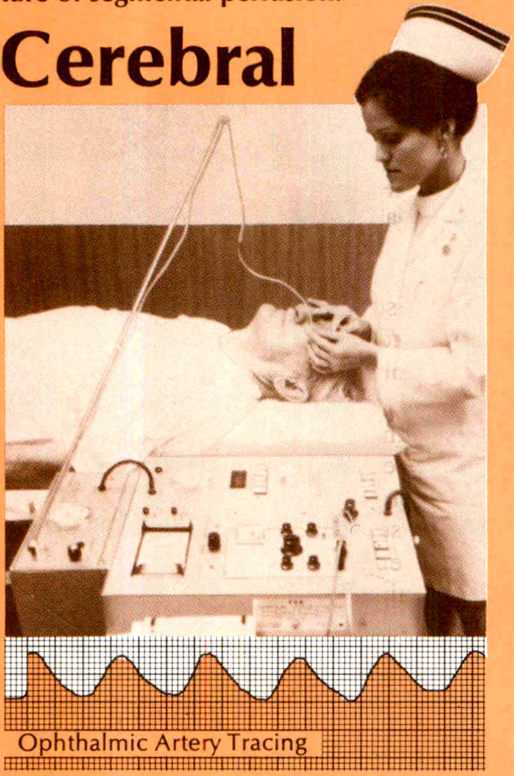
e COMBINED information of segmental PVR recordings and systolic pressure adient establishes a clinically accurate picture of segmental perfusion.

Venous



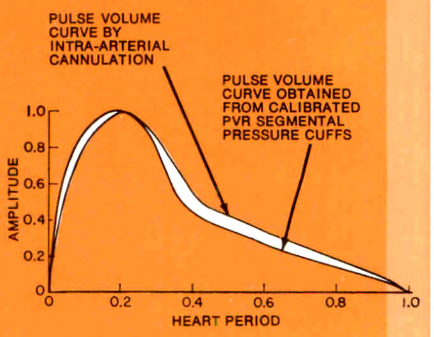
A 15-point scale provides quantitative criteria for the identification of increased deep venous resistance.

Cerebral



Ophthalmic Artery Tracing

Ophthalmic artery pressure is read directly on the OPG Attachment of the PVR for the evaluation of collateral circulation to each eye, and its respective cerebral hemisphere.



Comparison of pressure contours obtained with the PVR and direct cannulation of the common femoral artery.

EXCELLENT LONG-TERM
REPRODUCIBILITY AND
CALIBRATED ACCURACY BY
QUANTITATIVE SEGMENTAL
CUFF TECHNIQUE

The CLINICAL PROCEDURES for the Evaluation of Peripheral Vascular Disease based on the Pulse Volume Recorder (PVR®) described here, have been qualified for reimbursement for In- and Out-Patients under:

- Various non-profit hospital and medical-surgical service plans • Medicare • Veterans Benefits • Commercial Insurance Companies

LSI **For In-Hospital use or Office-Based Practice.**

References, bibliography, and details on request.

Life Sciences Inc.
270 Greenwich Avenue
Greenwich, Connecticut 06830 U.S.A.
Tel. 203 869-2011

*As Developed by The Vascular Laboratory, Dept. of Surgery, Massachusetts General Hospital, Boston, Mass.

ANNALS OF SURGERY

Vol. 187 January 1978 No. 1

Neonatal Necrotizing Enterocolitis

Therapeutic Decisions Based upon Clinical Staging

MARTIN J. BELL, M.D., JESSIE L. TERNBERG, M.D., RALPH D. FEIGIN, M.D., JAMES P. KEATING, M.D., RICHARD MARSHALL, M.D., LESLIE BARTON, M.D., THOMAS BROTHERTON, M.S., M(ASCP)

From the Departments of Surgery and Pediatrics, Divisions of Pediatric Surgery, Infectious Disease, Gastroenterology, and Neonatology, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri

A method of clinical staging for infants with necrotizing enterocolitis (NEC) is proposed. On the basis of assigned stage at the time of diagnosis, 48 infants were treated with graded intervention. For Stage I infants, vigorous diagnostic and supportive measures are appropriate. Stage II infants are treated medically, including parenteral and gavage aminoglycoside antibiotic, and Stage III patients require operation. All Stage I patients survived, and 32 of 38 Stage II and III patients (85%) survived the acute episode of NEC. Bacteriologic evaluation of the gastrointestinal microflora in these neonates has revealed a wide range of enteric organisms including anaerobes. Enteric organisms were cultured from the blood of four infants dying of NEC. Sequential cultures of enteric organisms reveal an alteration of flora during gavage antibiotic therapy. These studies support the use of combination antimicrobial therapy in the treatment of infants with NEC.

AFTER A DECADE OF STUDY, the precise etiology and pathophysiology of neonatal necrotizing enterocolitis (NEC) remain unclear. Numerous reports implicating various factors and perinatal influences have been presented.[1,2,4,6,13,16,18,26,27] At the present time, no proven preventive measures have been developed, although one study suggests that prophylactic use of kanamycin in feedings may decrease the incidence of the disease.[10] Current practice emphasizes early recognition and vigorous efforts to minimize the impact of the illness.

Necrotizing enterocolitis can be recognized at various stages; a spectrum exists between a fulminant form, progressing to intestinal necrosis in 12–24 hours, and a more slowly evolving and benign form.[15,17] In fact, in its earliest stages NEC may resemble a number of other conditions prevalent in the neonatal population.

Comparison of the results of various treatment programs for NEC is hampered by the lack of a uniformly accepted set of diagnostic criteria and failure to delineate precisely the stage of the disease at the time of diagnosis. In the study to be described, a simple classification system has been applied in an effort to effect uniformity in the therapeutic decisions which have been made in the management of these infants.

Materials and Methods

The study group was derived from the newborn population hospitalized at St. Louis Children's Hospital Neonatal Intensive Care Unit and the nurseries of Barnes Hospital. Between 1968 and 1975, 97 patients were evaluated and treated for NEC. During an 18 month period from July, 1974 through December, 1975, 48 infants were classified and treated in a prospective fashion, and these infants form the basis of this report. One or more of the authors evaluated all infants at the time that the diagnosis of NEC was first entertained.

Reprint requests: Martin J. Bell, M.D., Division of Pediatric Surgery, St. Louis Children's Hospital, 500 South Kingshighway, St. Louis, Missouri 63110.

Supported by The Life Seekers, Inc., St. Louis, Missouri.

0003-4932-78-0100-0001-0085 © J.B. Lippincott Company

TABLE 1. *NEC Staging System Based upon Historical, Clinical and Radiographic Data*

STAGE I (Suspect)

a. Any one or more historical factors producing perinatal stress.
b. Systemic manifestations—temperature instability, lethargy, apnea, bradycardia.
c. Gastrointestinal manifestations—poor feeding, increasing pregavage residuals, emesis (may be bilious or test positive for occult blood) mild abdominal distension, occult blood may be present in stool (no fissure).
d. Abdominal radiographs show distension with mild ileus.

STAGE II (Definite)

a. Any one or more historical factors.
b. Above signs and symptoms plus persistent occult or gross gastrointestinal bleeding; marked abdominal distension.
c. Abdominal radiographs show significant intestinal distension with ileus; small bowel separation (edema in bowel wall or peritoneal fluid), unchanging or persistent "rigid" bowel loops, pneumatosis intestinalis, portal vein gas.

STAGE III (Advanced)

a. Any one or more historical factors.
b. Above signs and symptoms plus deterioration of vital signs, evidence of septic shock or marked gastrointestinal hemorrhage.
c. Abdominal radiographs may show pneumoperitoneum in addition to others listed in II c.

Staging of NEC

The criteria utilized in this group for the diagnosis of NEC and for grading the severity of disease are summarized in Table 1.

Stage I. An infant with these features may be designated as a case of suspected NEC. In order to exclude other neonatal disorders studies including bacterial cultures, electrolyte analysis, scrutiny of maternal drug history, coagulation studies, and contrast studies of the gastrointestinal tract are required.

Stage II. Other patients may be recognized as having NEC with greater certainty. Unequivocal malfunction of the gastrointestinal tract is demonstrated clinically and by radiographic evaluation. Other disorders such as malrotation and volvulus and Hirschsprung's disease must be excluded. These patients are designated as definite cases of NEC.

Stage III. Patients in an advanced stage of disease demonstrate evidence of bowel necrosis, peritonitis and septic shock. However, a small group of infants with NEC may have a less severe clinical course but radiographic evaluation shows pneumoperitoneum.

Description of Patients

The 48 patients in the study group are characterized in Table 2. Commercially prepared 20 calorie per ounce formula had been fed to 43 infants. Two had been fed 24 calorie formula,* one had had 13 calorie formula, one only sterile water and one received no feedings prior to the onset of symptoms.

Treatment

Patients were treated on the basis of the assigned grade of severity of NEC when the child was encountered.

Stage I. Evaluation of these suspect patients included cultures of blood, urine obtained by suprapubic bladder puncture, cerebrospinal fluid, stool and gastric aspirates. In addition, complete blood count, platelet count, blood gases and pH, serum electrolytes and glucose and blood urea nitrogen were obtained. Stool and gastric content were examined for the presence of blood. Feedings were discontinued and intravenous fluids provided. Nasogastric decompression with a #10 French sump tube to intermittent suction was initiated, and intravenous antibiotics, if not already in use, were

TABLE 2. *Characterization of Patients by Clinical Stage. Signs and Symptoms Expressed as a Per Cent*

	Stage		
	I	II	III
Number of patients	10	33	5
Sex			
Male	70	57	60
Female	30	43	40
Race			
Caucasian	50	36	60
Black	50	64	40
Gestational Age (wks)			
Mean	34	33	33
Range	29–40	26–40	30–40
Small for Gestational Age	40	33	40
Birthweight (gm)			
Mean	1780	1610	1680
Range	1000–3660	780–3620	945–3180
Perinatal History			
Pulmonary disease	40	80	60
Cardiopulmonary or Temp. instability	50	36	20
Abnormalities of labor and delivery	20	36	60
Multiple births	40	27	20
Infection (Maternal or infant)	30	25	60
Umbilical catheter or exchange	30	33	40
Signs and Symptoms			
Abdominal distension	60	66	100
Increased pregavage aspirate	60	30	40
Emesis	20	42	40
Gastrointestinal bleeding	60	69	60
Lethargy, cardiopulmonary or temp. instability	30	33	60
Radiographic Findings			
Ileus and distension	100	42	80
Interloop thickening	20	18	0
Pneumatosis intestinalis	0	78	60
Portal vein gas	0	9	0
Pneumoperitoneum	0	0	60

---

* Similac (Ross).

started. The infants were observed carefully for signs of progression of disease. Abdominal films were obtained at least daily for several days.

Stage II. If a definite diagnosis of NEC was made the measures outlined above were initiated. In addition, an aminoglycoside antibiotic (kanamycin or gentamicin), was delivered topically to the gastrointestinal tract by means of intermittent nasogastric gavage. Abdominal radiographs, including a left lateral decubitus film, were obtained at six to eight hour intervals initially and less frequently when clinical and radiographic improvement was noted. Treatment was continued for 48 hours after resolution of all clinical and radiographic abnormalities. At that time, the nasogastric suction and the gavage antibiotic were discontinued and the child observed for a further 24 hours. Feedings with dilute glucose-casein-medium chain triglyceride* formula was then begun. Parenteral antibiotics were continued for 10–14 days from the onset of symptoms, presuming the presence of sepsis secondary to bacterial invasion of injured intestine. Occult blood was frequently present in the stool of these infants for one to two weeks after the acute episode. Serial serum aminoglycoside concentrations were measured at intervals during the course of therapy.

Stage III. Operative intervention was undertaken because of intestinal perforation, severe gastrointestinal hemorrhage, deterioration of vital signs, or failure to respond to the therapy outlined for patients in Stage II. Operative therapy included diversion with resection of gangrenous or perforated intestine. Peritoneal cultures and saline lavage of the peritoneal cavity were performed and a tube gastrostomy was placed.

Antibiotic Therapy

Thirty-six of the 48 patients were receiving antibiotic therapy before the onset of NEC. Most commonly, combinations of a semisynthetic penicillin, generally ampicillin (150–200 mg/Kg/24h), and an aminoglycoside, usually kanamycin (15 mg/Kg/24h) had been used. In the earliest months of the study period, when the diagnosis of NEC was made, this combination was continued if already in use, and gavage therapy with kanamycin (30 mg/Kg/24h in six divided doses) was carried out in seven patients.

From December, 1974 through the conclusion of this study period, parenteral antibiotics were changed to clindamycin (30 mg/Kg/24h) and gentamicin (5–7.5 mg/Kg/24h). Gavage therapy with gentamicin (10–15 mg/Kg/24h in six divided doses) was provided in addition to the parenteral therapy for 25 patients. Gavage aminoglycoside treatment was continued for a period of three to five days (mean four days).

Serum aminoglycoside concentrations were measured in 20 of the 33 patients classified as Stage II. They were not studied in the other groups. Aminoglycoside serum concentrations were measured by the method described by Smith, et al.[20] Samples were obtained during the second 24 hour period of gavage therapy before and 15–30 minutes after intravenous doses and before and one to two hours after gavage. Seventy-one individual serum determinations were performed, a mean of 3.5 determinations for each patient studied. Pretreatment concentrations were obtained in eight infants who were already on parenteral aminoglycosides at the time of diagnosis of NEC.

Bacteriologic Studies

Blood, gastric and fecal cultures were processed for both aerobic and anaerobic organisms in most cases. Blood cultures were obtained at the time of initial evaluation of the patient for NEC from all ten Stage I patients, 32 of 33 Stage II patients, and four of five Stage III patients.

Before starting gavage antibiotic therapy, nasogastric aspirate and rectal swab for fecal culture were obtained. Initial gastric aspirate cultures were obtained from five of ten Stage I, 22 of 33 Stage II, and one of five Stage III patients. Initial stool cultures were obtained from six of ten Stage I patients, 20 of 33 Stage II patients, and three of five Stage III patients. Sequential stool and gastric culture studies were performed on one or two subsequent days during gavage antibiotic therapy in 13 patients.

Operative Therapy

Operative procedures were performed on nine patients (19%) for indications of perforation in five, clinical deterioration in three and profuse lower gastrointestinal hemorrhage in one infant. Segmental resection of the most severely affected bowel, including the site of perforation, and proximal diversion with construction of a distal mucous fistula was performed in seven patients. Mikulicz enteroenterostomy at the site of perforation was performed in one patient. One child underwent only laparotomy at which time the entire colon and small bowel were found to be involved with NEC.

Results

Complications

Complications associated with NEC and its treatment were noted in ten infants who survived the acute phase of the illness. Intestinal strictures occurred in three patients after successful medical therapy. Operative relief of obstruction was required in all three; one infant died. Another child required revision of a stenotic ileostomy stoma.

---

* Pregestimil (Mead-Johnson).

Four infants developed complications during treatment with total parenteral nutrition. A prolonged, but self limited, cholestatic process occurred in one infant. One child developed an unexplained hemolytic anemia. Right atrial thrombosis with microscopic pulmonary thromboembolism, and perforation of a catheter into the right hemithorax occurred in two other infants. Two infants had recurrent, but less severe episodes of NEC when feedings were resumed.

Mortality

Among the 48 patients treated during this period, 36 survived and 12 died, a raw mortality rate of 25%. However, this figure requires further scrutiny. Since the Stage I patients may not have had NEC, or a very mild form of the disease, and all survived, one might focus on the 38 infants in Stages II and III. In that group mortality directly attributable to NEC may be derived from the following consideration. Of the 12 infants who died, five deaths occurred during the acute phase of NEC and one following a secondary obstructive episode. The remaining six infants died of severe pulmonary disease having recovered from NEC under the treatment program previously outlined. Pulmonary mortality was at an interval after recovery from NEC which suggests that NEC did not contribute to the ultimate demise of the patient. Therefore, the mortality attributable to NEC was six of 38, or 15%.

Retrospective examination of the clinical and cultural characteristics of the infants who died of NEC permits identification of the infants at greatest risk. There were three females, three males, three caucasian and three black. Weights ranged from 860 to 1540 grams with a mean weight of 1225 g. Four of six (67%) were small for gestational age, the gestational age ranging from 30 to 35 weeks. This contrasts with the surviving infants whose mean weight was 1810 g, and among whom only 27% were small for gestation age. Although suggestive, these differences are not statistically significant in this small series. Four of the six infants who died of NEC had positive blood cultures at the time of or immediately before the onset of symptoms. Among the 26 surviving infants, 22 had blood cultures obtained at the onset of NEC symptoms. Twenty had no growth and two were considered contaminated. The organisms grown from the blood of infants dying of NEC were all enteric organisms. Three of the six infants who expired had portal venous gas seen on radiographic examinations of the abdomen. Also characteristic of the infants who died of NEC was the rapidly progressive and virulent course which the disease followed both before and after operation. Prominent in these infants was the presence of disseminated intravascular coagulation and evidence of pulmonary and intracranial hemorrhage.

Thirty-three Stage II patients were treated initially as outlined previously, including gavage antibiotics in 32. Five of these infants (15%) developed progressive disease and advanced to Stage III status. Indications for operation were evidence of perforation in two, and rapid deterioration in three. Four of these infants died as a result of NEC. One Stage II infant, who survived the initial episode, died after developing an intestinal

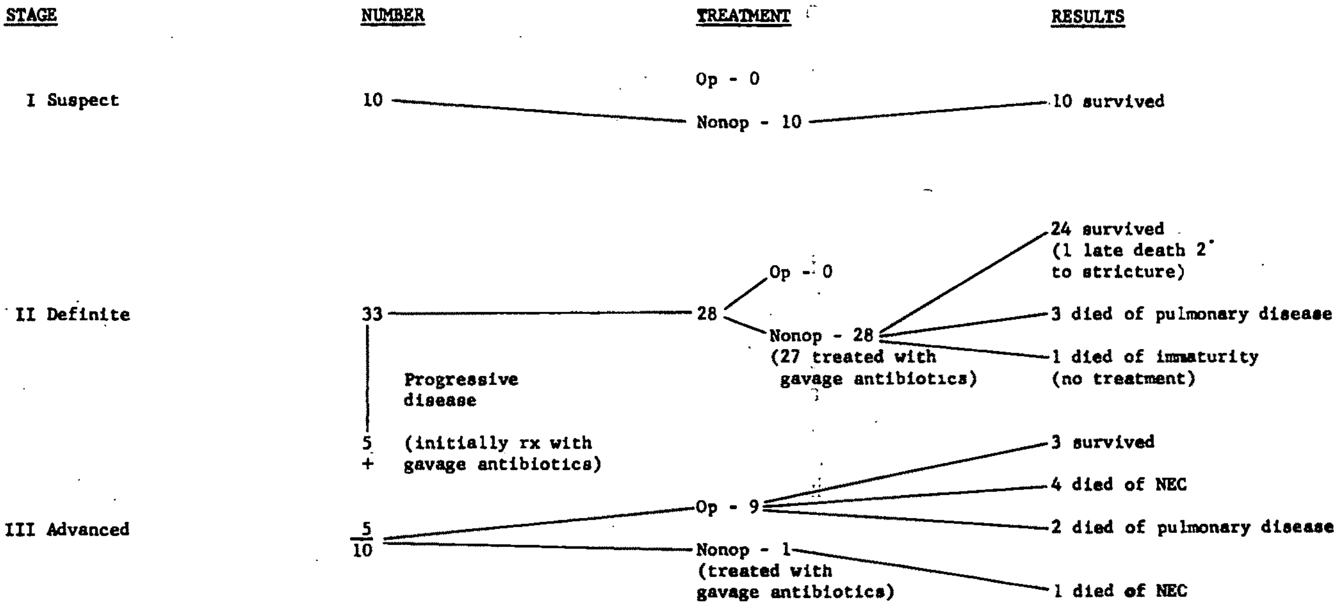


FIG. 1. Results of treatment.

stricture. Mortality for Stage II disease is therefore 15%.

Five infants initially were encountered at Stage III, of whom four underwent immediate laparotomy and two survived. Another child, who was treated inappropriately by non-operative means only, deteriorated rapidly and expired. Mortality for Stage III disease is therefore 60%. Of all the infants who ultimately satisfied the criteria for Stage III (ten), five (50%) died of NEC. These results are summarized in Figure 1.

Bacteriology of NEC

Blood cultures. Blood samples obtained from all ten Stage I patients were sterile. Two of the blood cultures obtained in 32 of 33 Stage II patients were positive; one yielded *E. coli*, and the other *K. pneumoniae*. Both these children died of NEC. Blood cultures were positive in three patients in Stage III NEC. Organisms grown were *Peptostreptococcus*, gamma streptococcus and alpha streptococcus, *E. coli* and *Streptococcus agalactiae*. All three of these infants died, two of NEC.

Gastric cultures. The gastric aspirate from three of five Stage I patients were sterile. Gastric aspirate cultures from the two remaining patients grew gamma streptococcus, and *S. epidermidis*. The gastric aspirate cultures from eight of 22 stage II patients were sterile. The remaining 13 patients grew one or more organisms; these are listed in Table 3. Only one infant with Stage III disease had a gastric aspirate culture, which grew *E. coli*, *K. pneumoniae*, *Streptococcus agalactiae* and *S. epidermidis*.

Stool cultures. Cultures of stool were obtained from 38 patients. One was reported to have no growth. No pathogenic organisms were identified among stool cultures. Twenty-two patients had fecal culture studied to recover all organisms present. The organisms encountered in 32 patients of Stage II and III are listed in Table 3. Most patients had two or more organisms isolated, and seven (13%) anaerobic isolates were found among a total of 52 isolates.

Sequential fecal cultures were studied in 13 patients receiving gentamicin gavage. A change in the fecal microflora during the course of therapy was noted (Table 4). Most notable was the reduction in the number of gram negative species isolated and a relative increase in gram positive organisms and yeast.

Serum aminoglycoside studies. Serum concentration of aminoglycoside antibiotics was obtained in eight patients who already were receiving aminoglycoside therapy at the time of diagnosis of NEC. On four occasions the serum concentration of aminoglycosides was greater than the maximum serum concentration expected with the doses previously mentioned (10 yg/ml). All four patients were receiving kanamycin parenterally only, and the dosage schedules for kanamycin in all neonates have since been revised. Five of 71 serum specimens obtained from patients receiving combined gavage and intravenous gentamicin had concentrations above 10.0 yg/ml. All but one of these patients had other serum aminoglycoside concentrations in the usual therapeutic range.

TABLE 3. *Gastric and Fecal Organisms Acquired from Stage II and III Patients (Number of Isolates)*

Gastric Organisms	Number of Isolates	Fecal Organisms	Number of Isolates
S. epidermidis	8	*S. epidermidis*	10
S. aureus	2	*S. aureus*	1
Gamma streptococcus	4	Gp D strep enterococcus	4
K. pneumoniae	8	*S. agalactiae*	1
E. coli	3	*K. pneumoniae*	10
citrobacter	1	*E. coli*	15
B. fragilis	1	*E. aerogenes*	1
B. oralis	1	citrobacter	1
saccharomyces	1	corynebacterium	1
		B. fragilis	5
		Cl. perfringens	1
		peptostreptococcus	1
		Veillonella parvula	1

Discussion

During an 18 month period we have studied and treated 48 patients with NEC. An effort was made to assess the severity of the illness and to provide graded intervention based on that assessment. We have designated these stages in NEC as Stage I (Suspect), Stage II (Definite) and Stage III (Advanced). Infants who were classified Stage I were provided supportive care and intensive diagnostic evaluation was carried out to exclude other causes of their symptoms. Infants classified as Stage II were treated medically, with both parenteral and topical antibiotic therapy delivered by nasogastric gavage. Infants with Stage III disease required operative treatment. Use of this staging system will allow valid comparison of current and future efforts in the management of infants with NEC.

No patients who were considered suspect for NEC (Stage I) progressed to more advanced stages. While

TABLE 4. *Changes in the Fecal Microflora of Infants Treated with Aminoglycoside Gavage*

	Culture #1	Culture #2	Culture #3
Number of isolates	29	31	20
Gram negative isolates	20	16	9
Gram positive isolates	9	14	7
Anaerobic isolates	4	3	3
Yeast	0	1	4

they may indeed have had early and mild NEC, easily aborted by simple means, they may not truly have had NEC. Clarification will require the development of a more specific method of early diagnosis. Hence they have been discarded from further evaluation of our therapeutic efforts.

The 85% survival of Stage II patients is encouraging; these results compare favorably to the mortality rates reported by others.[7,9,11,18,19,22,23,25] However, identification of infants first classified as Stage II who then progress to Stage III is a continuing challenge. Twenty-six of 33 Stage II patients demonstrated pneumatosis intestinalis, but only five of these advanced to Stage III. Three infants with portal vein gas were among this group. While this finding is ominous, other patients not included in this report have shown no progression of disease during non-operative therapy. Instability of vital signs, thrombocytopenia, metabolic acidosis, or persistent fixed distended loops of bowel all suggest progressive disease. Unfortunately, intestinal necrosis and perforation may have developed already when these signs appear. Even less encouraging are the results obtained in the infants with advanced disease who require surgical intervention. Some of these infants developed their symptoms and died within 12–18 hours. There appears to be no effective therapy currently available for this fulminant form of NEC.

Thirty-two patients received gavage aminoglycoside antibiotic therapy in addition to the other supportive care generally provided for infants with NEC. Several of these infants deteriorated rapidly after the initial evaluation, and two developed perforation. Twenty-four of these patients are alive and well at the time of this report with no obvious functional intestinal insufficiency or other abnormalities related to NEC.

The bacteriologic studies reported here support the use of a combination of antibiotics effective against the microflora usually resident in the gastrointestinal tract of these neonatal patients. A wide range of enteric organisms including anaerobes were found. Gastric aspirates contained an unusual distribution of enteric gram negative organisms and anaerobes in a number of patients. Blood cultures grew enteric organisms in four of six infants who died of NEC. Since patients with NEC may have an alteration in the bowel wall permitting entrance of microorganisms into the circulation, the use of antibiotics effective against the organisms usually present seems reasonable. In patients with evidence of perforation such therapy is mandatory. The studies of Weinstein and associates support the use of an aminoglycoside and clindamycin as the regimen which provided the most effective therapy for peritonitis.[28]

The precise role of the enteric microflora in the pathophysiology of NEC is unclear. There are several reports in which specific organisms have been implicated in patients with NEC.[11,12,18,21] Our data fail to support this possibility in our patients. However, other investigations have suggested that suppression of the enteric microflora might contribute to improvement in the results of treatment of NEC.[3,5] Preliminary evaluation of sequential enteric cultures in a small number of patients reveals a change in the microflora during the course of aminoglycoside gavage. A quantitative effect also may have been derived from this therapy but this was not evaluated in the current study. A control group for Stage II patients who receive no gavage aminoglycoside has not been included which makes assessment of this particular element of care impossible. This aspect of treatment deserves further study. Similarly, further evaluation of the gastrointestinal microflora in NEC is indicated. A comparison of the microflora of infants with NEC with normal term infants and other ill infants is in process.

It continues to be our impression that NEC is best treated by early, vigorous medical means, and that operative intervention should be reserved for those patients who fail to respond, or in whom complications supervene.

References

1. Barlow, B. and Santulli, T.: Importance of Multiple Episodes of Hypoxia or Cold Stress on the Development of Enterocolitis in an Animal Model. Surgery, 77:687, 1975.
2. Barlow, B., Santulli, T., Heird, W., et al.: An Experimental Study of Acute Neonatal Enterocolitis: The Importance of Breast Milk. J. Pediatr. Surg., 9:587, 1974.
3. Bell, M., Kosloske, A., Benton, C. and Martin, L.: Neonatal Necrotizing Enterocolitis: Prevention of Perforation. J. Pediatr. Surg., 8:601, 1973.
4. Book, L. S., Herbst, J. J., Atherton, S. O. and Jung, A. L.: Necrotizing Enterocolitis in Low Birth Weight Infants Fed on Elemental Formula. J. Pediatr. 87:602, 1975.
5. Cohn, I., Jr.: Intestinal Antisepsis. Springfield, Charles C Thomas, 1968.
6. DeLemos, R. A., Rogers, J. H. and McLaughlin, G. W.: Experimental Production of Necrotizing Enterocolitis. Pediatr. Res., 8:380/106, 1974.
7. DeLuca, F. G. and Wesselhoeft, C. W.: Neonatal Necrotizing Enterocolitis Am. J. Surg., 127:440, 1974.
8. Dowell, V. R. and Hawkins, T. M., 1974, Laboratory Methods in Anarobic Bacteriology, Center for Disease Control Laboratory Manual, Center for Disease Control, Atlanta, Georgia.
9. Dudgeon, D. L., Coran, A. G., Lauppe, F. A., et al.: Surgical Management of Acute Necrotizing Enterocolitis in Infancy. J. Pediatr. Surg., 8:607, 1973.
10. Egan, E., Mantilla, G., Nelson, R. and Eitzman, D.: A Prospective Controlled Trail of Oral Kanamycin in the Prevention of Neonatal Necrotizing Enterocolitis, J. Pediatr. 89:467, 1976.
11. Frantz, I. D., III, L'Heureux, P. L., Engel, R. R. and Hunt, C. E.: Necrotizing Enterocolitis, J. Pediatr. 86:259, 1975.
12. Hill, H. R., Hunt, C. E. and Matsen, J. M.: Nosocomial Colonization with Klebsiella, Type 26, In a Neonatal Intensive Care Unit Associated with an Outbreak of Sepsis, Meningitis, and Necrotizing Enterocolitis, J. Pediatr. 85:415, 1974.

13. Hillman, L. S., Goodwin, S. L. and Sherman, W.: Identification and Measurement of Plasticizer in Neonatal Tissue after Umbilical Catheters and Blood Products. N. Engl. J. Med., 292:381, 1975.
14. Holdeman, L. V. and Moore, W. E. C. (eds.) Anaerobe Laboratory Manual, Anaerobe Laboratory, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, 1973.
15. Leonidas, J. and Hall, R.: Neonatal Pneumatosis Coli: A Mild Form of Neonatal Necrotizing Enterocolitis, J. Pediatr. 89:456, 1976.
16. Lloyd, J.: The Etiology of Gastrointestinal Perforation in the Newborn, J. Pediatr. Surg., 4:77, 1969.
17. Richmond, J. and Mikity, V.: Benign Form of Necrotizing Enterocolitis. Am. J. Roentgenol. Radium Ther. Nucl. Med., 123:301, 1975.
18. Roback, S., Foker, J., Frantz, I., et al.: Necrotizing Enterocolitis: An Emerging Entity in the Regional Infant Intensive Care Facility. Arch. Surg., 109:314, 1974.
19. Santulli, T. V., Schullinger, J. N., Heird, W. C., et al.: Acute Necrotizing Enterocolitis in Infancy: A Review of 64 Cases, Pediatrics., 55:376, 1975.
20. Smith, D., Van Otto, B. and Smith, A.: A Rapid Chemical Assay for Gentamicin. N. Engl. J. Med., 286:583, 1972.
21. Speer, M. E., Taber, L. H., Yow, M. D., et al.: Fulminant Neonatal Sepsis and Necrotizing Enterocolitis Associated with a Nonenteropathogenic Strain of Escherichia Coli. J. Pediatr., 89:91, 1976.
22. Stevenson, J. K., Graham, C. B., Oliver, T. K. and Goldenberg, V. E.: Neonatal Necrotizing Enterocolitis: A Report of Twenty-One Cases with Fourteen Survivors. Am. J. Surg., 118:260, 1969.
23. Stevenson, J. K., Oliver, T. K., Graham, C. B., et al.: Aggressive Treatment of Neonatal Necrotizing Enterocolitis, J. Pediatr. Surg., 6:28, 1971.
24. Sutter, V. L., Atteberry, H. R., Rosenblatt, J. E., et al.: Anaerobic Bacteriology Manual, University of California, Los Angeles, 1972.
25. Torma, M. J., DeLemos, R. A., Rogers, J. R. and Diserens, H. W.: Necrotizing Enterocolitis in Infants: Analysis of Forty-five Consecutive Cases. Am. J. Surg., 126:758, 1973.
26. Touloukian, R., Kader, A. and Spencer, R.: The Gastrointestinal Complication of Neonatal Umbilical Venous Exchange Transfusion: A Clinical and Experimental Study. Pediatrics, 51:36, 1973.
27. Touloukian, R. J., Posch, J. N. and Spencer, R.: The Pathogenesis of Ischemic Gastroenterocolitis of the Neonate: Selective Gut Mucosal Ischemia in Asphyxiated Neonatal Piglets. J. Pediatr. Surg., 7:194, 1972.
28. Weinstein, W. M., Onderdonk, A. B., Bartlett, J. G., et al.: Antimicrobial Therapy of Experimental Intra-abdominal Sepsis, J. Infect. Dis., 132:282, 1975.

Announcement

The appearance of the code at the bottom of the first page of an article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for personal or internal use of specific clients. This consent is given on the condition, however, that the copier paid the stated per-copy fee through the Copyright Clearance Center Inc., P.O. Box 765, Schenectady, N. Y. 12301, for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

Multiple Carcinomas of the Large Bowel:

A Natural Experiment in Etiology and Pathogenesis

WARREN E. ENKER, M.D., F.A.C.S.,* SLOBODAN DRAGACEVIC, M.D.†

From the Dept. of Surgery, University of Chicago Pritzker School of Medicine, Chicago, Illinois

One hundred twenty-one patients with two or more large bowel cancers have been studied. An evaluation of the site of incidence of second cancers in patients presenting with metachronous disease supports the concept that increased delivery of bile acids to the colon may play a rôle in tumor pathogenesis. Because of the extremely high incidence of advanced tumors in patients with metachronous disease, every effort should be made to identify those patients who should undergo a preventive total abdominal colectomy. Newer methods with increased sensitivity are required to improve the follow-up of patients who are prone to develop second neoplasms of the large bowel.

IT IS IMPORTANT TO EXAMINE clinical material which may support or refute current concepts of carcinogenesis. In cancer of the colon, various etiologic factors have now been identified. These may include roles for hydrazine related carcinogens,[7] dietary fat,[6] and endogenous promoters of carcinogenesis such as bile acids and fecal flora.[3] Nigro has shown that the increased delivery of bile acids to the colon is associated with increased tumorigenesis.[5] While elevated fecal bile acids are present in patients with colorectal cancer, it remains uncertain whether these elevated values are causative or incidental to the issue of carcinogenesis. A clinical setting in which to examine the role of bile acids in promoting carcinogenesis would be helpful.

In man, resection of the ileum is associated with measurable increases in bile acid delivery to the colon.[8] These findings may even be present in limited ileal resections of as little as 20 cm.[4] While lesser resections might not produce measurable changes in bile acid absorption, subtle changes such as an increase in colon carcinogenesis might evolve over years of low-level alteration.

Since resection of the ileum is a feature of right hemicolectomy for cancers of the cecum or ascending colon we have examined the incidence of second primary cancers in patients who have had a previous ileal resection as a part of their first hemicolectomy for cancer. We postulate that if the incidence of left-sided second primary cancers in patients with metachronous large bowel cancer is higher than the incidence of right-sided cancers in patients undergoing an initial left colectomy, the theories concerning bile acids in colon carcinogenesis would be consistent with clinical experience.

Materials and Methods

From 1940 to 1971, 3,842 patients with large bowel cancer were enrolled in The University of Chicago Registry of Neoplastic Diseases. A retrospective examination of these data reveal that 121 patients had multiple primary large bowel cancers (3.14%). Of these, 68 patients (56.2%) presented with synchronous lesions while 53 patients (43.8%) presented with metachronous or nonsimultaneous lesions. All staging was performed in accordance with the Modified Dukes' classification of Astler and Coller.[1] For the purpose of examining incidence of disease, the data was examined both including and excluding Dukes' A lesions (Carcinoma *in situ*).

All of the primary cancers were classified as being located either on the right side, or on the left side, or as being located in the transverse colon. Right-sided lesions included carcinomas of the cecum, ascending colon, or hepatic flexure. Left-sided lesions included those found at the splenic flexure, descending colon, sigmoid, rectosigmoid, or rectum.

Synchronous Lesions

Sixty-eight patients presented with two or more synchronous large bowel cancers. There were 153 lesions in the 68 patients. Forty-six of the patients were male (67.6%) and 22 of the patients were female (32.4%).

---

* Associate Professor, Department of Surgery, Junior Faculty Clinical Fellow, American Cancer Society.

† Research Associate in Surgical Oncology.

0003-4932-78-0100-0008-0060 © J.B. Lippincott Company

The majority of the patients (84%) were 51 to 80 years of age at the time of presentation with a mean age of 62.2 years. An examination of the Modified Dukes' classification stage of the major lesion in each patient revealed that 79% of the patients either had full penetration of the bowel wall (Dukes' B_2), or the involvement of lymph nodes (Dukes' C_1 or C_2) at the time of presentation. Only three of 68 patients had lesions limited to the mucosa, while 54 of 68 patients had advanced, but curable lesions (stages B_2, C_1, and C_2) (Table 1). Twenty-three per cent of the patients presented with right-sided lesions while 67% had left-sided lesions. Lesions were limited to the transverse colon in 10% of the cases. Four patients (5.6%) had chronic ulcerative colitis, 13 patients (19.1%) had benign adenomas of the colon, and three of the 13 patients had multiple adenomas. Eleven of the patients (16.2%) had other malignant neoplasms unrelated to the large bowel.

The mean survival of patients presenting with synchronous large bowel cancers was 6.81 years. The five year survival of this group was 46.3%. This survival included an operative mortality of eight of the 68 patients, or 11.7%. The mean age of the patients dying as the result of operation was slightly higher at 67.9 years. Postoperative deaths were attributed to cardiopulmonary causes in five patients and peritonitis or confirmed anastomic disruption in three cases. Survival in this selected group is inferior to our previously reported survival of 60.9% for all patients under 70 years of age with large bowel cancer.[2]

Metachronous Lesions

Of the 121 patients with multiple large bowel cancers, 53 patients presented with multiple nonsimultaneous, or metachronous large bowel cancers. Of these, 31 patients (58.5%) were male, while 22 of the patients were female (41.5%). Six of the patients presented with two or more initial tumors and were excluded from further analysis because they fit into both the synchronous and the metachronous classification. This left a total of 47 patients for the examination regarding the incidence of multiple large bowel cancers.

TABLE 1. *Synchronous Large Bowel Cancers*

Stage of Major Lesion		
Modified Dukes' Classification	Number of Lesions	
A	3	
B_1	8	
B_2	30	79%*
C_1	5	
C_2	19	
D	3	
TOTAL	68	

* 54/68 Advanced but curable.

TABLE 2. *Metachronous Large Bowel Cancers*

Stage of Major Lesion		
Modified Dukes' Classification	Number of Lesions	
A	1	
B_1	2	
B_2	21	87%*
C_1	1	
C_2	19	
D	3	

* 41/47 Advanced but curable.

Three patients had chronic ulcerative colitis (5.7%) and 16 patients had one or more benign adenomas of the colon (30.2%). Nine patients (16.9%) had other malignant tumors unrelated to the large bowel.

An examination of the major lesion in each patient revealed that 41 of the 47 patients (87%) had advanced but curable lesions (Table 2). Twenty-one patients presented with full penetration of the bowel wall (Dukes' B_2) while 20 of the 47 patients presented with involvement of lymph nodes (Dukes' C_1 or C_2). Only one of 47 patients had lesions limited to the mucosa (Dukes' A).

The five year survival for all patients with metachronous disease after their first operation was 77.36% (41 of 53 patients) and the mean survival for all patients was 14 years and three months. Five year survival by stage of disease after resection of the first cancer was: Dukes A–66.7%, B_1–80%, B_2–92.3%, and C_2–55.5%. These figures included death from all causes.

Of the patients with metachronous large bowel cancers, 28 of 47 patients (60%) had their first lesion on the left side while 13 of the 47 patients had their first lesion on the right side (28%). The remaining six patients had their first lesion in the transverse colon.

Of the 28 patients who had their first resection on the left side, 12 patients subsequently developed their second primary carcinoma on the right side of the large bowel (43%). Of the 28 patients who had their first resection on the left side, 13 (46%) developed their second primary lesion in the remaining portion of the left side. In contrast, of the 13 patients who had their first resection on the right side of the colon, ten developed a second lesion in the left side of the colon (77%) (Table 3). Thus the incidence of second primary carcinomas in patients who first underwent an initial right-sided resection was much higher than the incidence of right-sided cancers in patients undergoing initial left colectomies, and was also higher than the initial incidence of left-sided lesions (60%). When the patients with Dukes' A lesions were removed from the

TABLE 3. *Metachronous Cancer "Conversion" Rate*

	Site of Initial Cancer		
	Right	Left	Transverse
	13 (28%)	28 (60%)	6
Site of Second Cancer			
Right	1	12 (43%)	2
Left	10 (77%)	13 (46%)	4
Transverse	2	3	

statistical evaluation, no essential change in incidence was discovered (Table 4).

Detection and Follow-up

An examination of the stage of the second lesion presenting in patients with metachronous large bowel cancers is revealing. The 53 patients with metachronous large bowel cancer were reviewed in order to evaluate the role of regular follow-up examination in the detection of their second tumor. The patients were divided into three categories: (1) regular follow-up (2) no regular follow-up and (3) no follow-up at all. Patients were categorized as having had regular follow-up if they had six-monthly physical examinations or proctoscopy and, at least, an annual barium enema. Patients who did not meet these criteria, but who were followed-up in some other fashion were designated as having had no regular follow-up. Patients who were completely devoid of scheduled office visits were classified as having had no follow-up at all.

Thirty-seven of the 53 patients (69.8%) were classified as having undergone regular follow-up examination. Of these, 18 patients had obvious clinical symptoms at the time their second tumor was discovered, while 19 of the patients had their tumors when they had no symptoms. This was accomplished by various screening methods at the time of annual or semiannual examination (Table 5). Over 50% of the patients receiving regular follow-up examination had their second tumor detected when these tumors were still asymptomatic. Of the patients with regular follow-up in whom lesions were discovered in the absence of symptoms, only nine of 19 (47.3%) had advanced lesions, compared to 14 of 18 patients in whom symptoms were present (77.7%). Overall, 27 of 37 patients with regular follow-up had Dukes B_2 or C lesions at laparotomy (62.1%) (Tables 6 and 7).

TABLE 4. *Metachronous Conversion Rate Influence of Dukes' A Lesions*

Conversion Rate	With Dukes' A	Without Dukes' A
Right to Left	77%	75%
Left to Right	43%	40%
Left to Left	46%	45%

TABLE 5. *Follow-up Examination*

		Regular Follow-up	No Regular Follow-up	No Follow-up
Symptoms	Yes	18	13	2
	No	19	1	0
Method of Diagnosis				
Ba Enema		19	11	1
Proctoscopy		10	2	1
Digital Rectal		4		
Abdominal Exam		1		
Laparotomy		3		
		—	—	—
	Total	37	14	2 = 53

Compared to irregular follow-up, careful follow-up examination resulted in the detection of 50% of the metachronous tumors in an asymptomatic state, with an overall 16% lower incidence of advanced lesions at the time of laparotomy. Compared to irregular follow-up, regular follow-up resulted in the detection of cancer in 52% of patients without any clinical symptoms. In the absence of symptoms, clinically advanced lesions were much fewer in number (47.3%) when compared to the stages of the tumors detected in patients not receiving careful follow-up (78.6% advanced).

Discussion

In general the survival of patients with more than one carcinoma of the colon at different times (metachronous lesions) is no different than that of the general population of patients. The survival of patients with synchronous lesions however, was considerably less than that of our normal population. (46.3% vs 60.9% of patients less than 70 years of age).[2] This may imply that survival was influenced by the number of simultaneous tumors, as well as by the advanced stages of the presenting tumors (79% B_2, C_1, or C_2).

Three additional points require emphasis. First,

TABLE 6. *Metachronous Large Bowel Cancer, Stage of Second Primary Cancer*

Modified Dukes' Classification	Regular Follow-up		No Regular Follow-up		No Follow-up
A	9		1		1
B_1	5		2		
B_2	12	23/37	6	11/14	1
C_1	3				
C_2	7		3		
D	1		2		
Advanced lesions	62.1%		78.6%		

TABLE 7. *Effect of Symptoms on the Stage of Disease at the Time of Detection in 37/53 Patients Receiving Regular Follow-up Examination*

Modified Dukes' Classification	Symptoms Present		Symptoms Absent	
A	2		7	
B_1	2		3	
B_2	7	14/18	5	9/19
C_1	3		0	
C_2	4		3	
D	0		1	
	18		19 = 37	
Advanced lesions	77.7%		47.3%	

there are many reasons why the incidence of left-sided second primary tumors might be higher than right-sided second primary tumors. These factors include all of the described features inherent in the etiology of colon cancer as well as the simple fact that the left colon as we have defined it has a larger surface area with a proportionately larger likelihood of tumor incidence.

In this instance, we have discounted the likelihood that surface area alone is the sole cause for the increase in second cancers, as the incidence of left-sided second primary tumors after right hemicolectomy is higher than the original incidence of left-sided lesions alone (77% vs 60%).

Regarding the other factors in colon carcinogenesis, it remains unlikely that alteration of dietary habits would have received a consistent emphasis in each of these individual patients over the 30 year period studied. Similarly, other than bile acid absorption in these postoperative patients, there are few data to support any other alteration in the lower GI tract which could clearly influence the pathophysiology of tumorigenesis as we know it.[5] We therefore conclude that these data concerning the incidence of second primary colon cancers in patients with metachronous disease support the concept that bile acids may act as promoters in the etiology of large bowel cancer.

Our second point relates to the prevention of lethal disease in patients known to be at high risk from multiple tumors. For this relatively small group of patients who present with more than one primary cancer or with the second of two or more subsequent primary cancers, the higher risk of colon neoplasia is clearly established. Up to 78.6% of the patients presenting with a second metachronous tumor had tumors which penetrated the complete thickness of the bowel wall or involved regional lymph nodes, and three of the 47 patients had distant metastases. Even in the asymptomatic state nearly 50% of the patients had advanced lesions. To prevent the recurrence of tumors of this serious magnitude, subtotal colectomy is strongly suggested for patients with synchronous or with second metachronous malignant tumors.

With regard to the detection of new cancers in patients already identified with large bowel cancer, it is evident that our inadequate and insensitive methods result in little if any reward in the detection of early carcinoma. As 78% of the patients with metachronous lesions presented with either Dukes' B_2 or C lesions, it must be evident that the sensitivity of our methods for the detection of early cancer of the large bowel is poor. Drastic efforts to improve our capabilities in this area are required, not only for this limited population but for the 101,000 new patients per year now afflicted by this disease.

Acknowledgment

The authors wish to acknowledge the University of Chicago Registry of Neoplastic Diseases and its director, Mrs. Florence Lowenstein for their capable assistance in the preparation of this report. We also thank Mrs. Harriett Hammonds who assisted in the preparation of the manuscript.

References

1. Astler, V. B. and Coller, F. A.: The Prognostic Significance of Direct Extension of Carcinoma of the Colon and Rectum. Am. Surg., 130:846, 1954.
2. Block, G. E. and Enker, W. E.: Survival After Operation for Rectal Carcinoma in Patients over 70 years of Age. Ann. Surg., 174:521, 1971.
3. Hill, M. J., Drasar, B. S., Williams, R. E. O., et al.: Faecal Bile, Acids, and Clostridia in Patients with Cancer of the Large Bowel. Lancet, p. 535. 1975.
4. Hofmann, A. F. and Poley, J. R.: Cholestyramine Treatment of Diarrhea Associated with Ileal Resection. N. Engl. J. Med., 281:397, 1969.
5. Nigro, N. D., Bhadrachari, N. and Chomchai, C. A rat Model for Studying Colonic Cancer: Effect of Cholestyramine on Induced Tumors. Dis. Colon Rectum, 16:438, 1973.
6. Reddy, B. S., Weisburger, J. H. and Wynder, E. L.: Effect of Dietary Fat Level and Dimethylhydrazine on Fecal Acid and Neutral Sterol Excretion and Colon Carcinogenesis in the Rat. J. Natl. Cancer Inst., 52:507, 1974.
7. Toth, B.: Synthetic and Naturally Occurring Hydrazines as Possible Cancer Causative Agents. Cancer Res., 35:3693, 1975.
8. Weser, E.: The Management of Patients After Small Bowel Resection. Gastroenterology, 71:146–150, 1976.

Reserpine Treatment of Raynaud's Disease

BIRGITTA ARNEKLO NOBIN, M.D., STEEN LEVIN NIELSEN, M.D., BO EKLØV, M.D., NIELS A. LASSEN, M.D.

Six patients with primary Raynaud's disease were investigated with magnification hand arteriography, measurement of finger systolic pressure and response to a newly devised local cooling test. They were treated with reserpine 0.5 mg injected into the brachial artery, and the clinical effects were followed by a scoring system and by the change in digital arterial tone during local cooling. The latter was registered as the change in systolic finger blood pressure measured indirectly by a finger-plethysmograph during stepwise decrease in finger temperature, until at a critical temperature complete closure of the digital arteries occurred. Shortly after injection the clinical condition improved, and closure of the digital arteries during local cooling was impeded. But within a week the cooling test showed a transient deterioration with closure of the digital arteries at the same or a somewhat higher temperature than before the reserpine injection. The clinical score followed this trend. According to animal experiments the shortlasting vascular effect of reserpine on primary Raynaud's disease might be due to depletion of the sympathetic nerve terminals for norepinephrine.

From the Department of Vascular Surgery, University Hospital, Lund, Sweden, and Departments of Clinical Physiology, Hvidovre and Bispebjerg Hospital, Copenhagen, Denmark

IN RECENT YEARS, reserpine administered perorally or intra-arterially has been claimed to be the most efficient drug treatment of the condition named primary Raynaud's disease.[1,2,5,11,12] The reported clinical effects are, however, diverging both as to relief of symptoms and to duration of the effect varying from few days to several months. The pathogenetic mechanism behind the Raynaud attack provoked by cold exposure is only partly understood.[2]

From the experimental studies performed some 50 years ago, Sir Thomas Lewis concluded that the clinical entity described by Maurice Raynaud in 1862 is basically caused by a complete closure of the digital arteries as a local response of the vascular smooth muscle to finger cooling.[4]

Closure of the digital arteries is a prerequisite for the 'doigt mort.' But sympathetic nervous activity is, at present, considered to be just as important as the local myogenic reaction.[6] This is the background for many proposed medical treatments comprising a variety of blocking drugs, and surgical intervention performed as sympathectomy in severe cases.[2] The effects of these treatments are, however, often discouraging with only transient clinical improvement and many side effects. The present study deals with the clinical and experimental evidence for the effect of reserpine given intra-arterially to patients with primary Raynaud's disease of varying severity as judged from arteriography and clinical symptoms. A newly developed method for measurement of digital arterial tone and closure temperature[7] allowed us to follow the acute and prolonged effects of reserpine treatment in a quantitative way.

Material and Methods

The patient material consists of six female patients, (mean age 37), referred to the department of vascular surgery for Raynaud's disease with a duration of more than five years (Table 1). They were normally menstruating, taking no vasoactive drugs or antiovulatory drugs. They all went through a thoroughly clinical examination comprising exact information on provoking factors and progression of the disease. Routinely venous blood samples were taken for analyses of hemoglobin thrombocytes, sedimentation rate, cryoglobulins, and cold agglutinin. Thyroid hormones (T_4 and TBG_m), immunological factors (AST, Latex fixation, Waaler-Rose reaction), and coagulation mechanism (fibrinogen, fibrinolysis and coagulation time) were analysed. X-ray of neck excluded cervical ribs.

During hospitalisation arteriography was performed as a combined aorto-cervical angiogram excluding proximal stenosis and a selective brachial arteriography demonstrating the small finger arteries by magnification. The latter was repeated after cooling of the hand by crushing an icecube for some minutes, and in three cases half an hour after injection of 0.5 mg reserpine through the catheter positioned in the brachial artery. The arteriograms were evaluated

---

Reprint request: Steen Levin Nielsen, Department of Clinical Physiology, Herlev Hospital, DK 2730 Herlev, Denmark.

Submitted for publication: February 1, 1977.

0003-4932-78-0100-0012-0075 © J.B. Lippincott Company

TABLE 1. *Clinical Data on Six Female Patients with Primary Raynaud's Disease for More than Five Years*

		Blood pressure			Clinical score			Closing temperature			
No.	Age	arm	finger	A-graphy	2–4 h	3–6 d	28 d	0	2–4 h	3–6 d	28 d
1	42	120/80	96	spasm/ stenosis	3	−1	0	21.5	16	22	19.5
2	36	100/68	98	spasm/ stenosis	1	0	−1	14.5	<10	17	20.5
3	33	124/70	35	spasm/ stenosis	5	0	—	15.0	<10	20.5	—
4	41	108/64	68	spasm/ stenosis	3	—	−1	21	16	—	19
5	37	118/80	42	spasm/ stenosis	3	—	6	<10	<10	—	15
6	32	105/70	90	spasm/ stenosis	1	1	0	<10	<10	<10	14.5

blindly by an experienced radiologist for organic stenoses or occlusions. The response to cold was taken as indication of a vasospatic moment (Table 1).

Fingersystolic blood pressure was measured using a specially devised plastic cuff on the midphalanges of ulnar fingers.[3] The volume increase on the outer phalanx when deflating the cuff was recorded by a mercury-in-silastic strain gauge. The finger exhibiting color changes most frequently was thereafter studied applying local cooling (Fig. 1). Finger systolic pressure was measured with a double inlet cuff before and after direct cooling of the midphalanx for periods of five minutes with circulation stopped by a tourniquet on the proximal phalanx. The temperature was lowered stepwise by 2.5–5° per step down to a level of 10°. At each temperature level finger systolic pressure was determined repeatedly until it regained the control level due to rewarming by the blood. Systolic blood pressure in the supplying arteries was estimated by measurement of finger systolic pressure in a control finger on the same hand. Arm systolic blood pressure was determined repeatedly to exclude changes in systemic blood pressure as measured by the conventional auscultatory technique. Temperature on fingers, in rooms and cooling devise was measured by thermocouples.

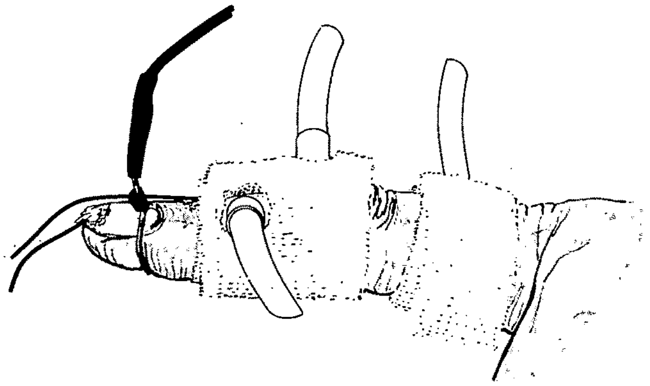


FIG. 1. Application of a blood pressure cuff on middle phalanx for local water cooling and measurement of systolic finger blood pressure by registration of a volume signal with a mercury-in-silastic strain gauge. During cooling the small cuff located on the proximal phalanx was used as tourniquet.

The cooling test was performed with the lightly dressed patient supine after a one half hour rest with room temperature at 23–25°. The patients were relaxed and sometimes fell asleep indicating absence of physical discomfort or distress. After initial investigation, 0.5 mg reserpine (Serpasil®, CIBA) diluted in 10 ml saline was given in the brachial artery. The injection was made in local anesthesia by direct puncture with a 21 gauge needle, the injection being performed in two to three minutes. Measurement of finger systolic pressure and reaction to local cold was repeated two to four hours after injection, three to eight days later and finally after 25–28 days. Information about the subjective effect was reported every second day in the ambulatory patients and clinical improvement of the injected hand was recorded by a scoring system (Table 2).

Results

During local cooling of the midphalanx a decrease in finger systolic pressure is observed indicating an in-

TABLE 2. *Clinical Scoring System for Complaints in Raynaud's Disease*

	Score			
Complaint	2	1	0	−1
Raynaud's phenomenon	absent	less frequent	unchanged	more frequent
Finger/hand temperature as compared to opposite		warmer	equal	cooler
Cyanosis of fingers	absent	decreased	unchanged	worsened
Tenderness of fingers	absent		unchanged	increased
Finger sores	healed		unchanged	worsened

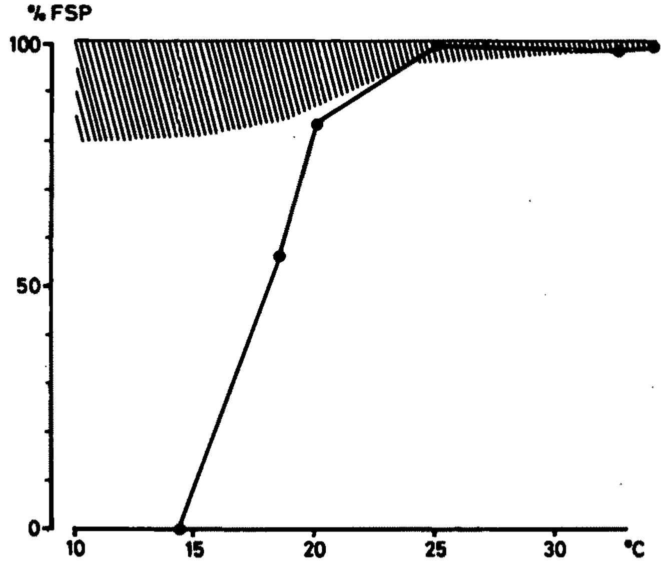


FIG. 2. Response to local cooling in a patient with primary Raynaud's disease measured as the percentage change in finger systolic blood pressure (FSP) during local cooling of the midphalanx of the right third finger. The variation in decrease of FSP during finger cooling in 15 normals are given by the hatching with 2.5 SD as lower limit.

crease in digital arterial tone (Fig. 2, case no. 2). It is seen that the arterial tone shows a gradual increase being significant compared to the normal group at 18.5° (threshold temperature) and leading to a sudden increase in tone giving complete closure of the digital arteries on the midphalanx at 14.5° (closure temperature). The hand arteriography for this patient is given in Figure 3.

For the six treated patients alterations in closing temperature and clinical score is given in Figure 4. The hand and forearm became pale eventually with pains immediately after the injection. At investigation two hours after injection, the hands were red, warm and sometimes a little edematous. Two patients (case 2 and case 3) had only clinical effect for about two days, the others had it for six to eight days (with the exception of case no. 5, who had only minor complaints of recurrence after four weeks). This patient had ulcers and tender fingertips before the injection as her main complaint, and the improvement was due to healing of the ulcers. She had been bilaterally sympathectomised three years earlier, and had only few Raynaud attacks.

In accordance with the clinical scoring the local cooling test showed an initial improvement after reserpine injection appearing as decrease in closing temperature. Within a week deterioration was observed in all cases by an increase in closing temperature and changes in threshold temperature followed this trend. Corresponding to the changes in closing temperature the digital arterial tone measured at 20° showed an initial decrease after reserpine injection followed by an increase to the control level (Fig. 5). This indicates that

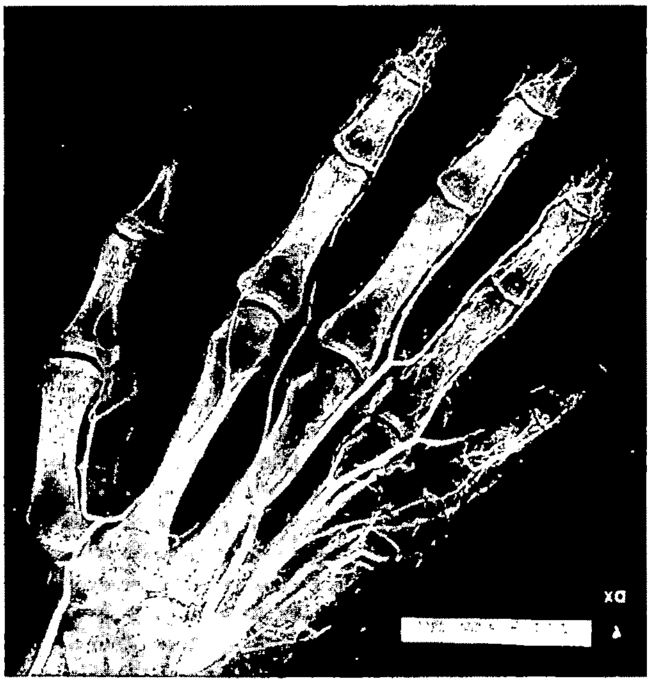


FIG. 3. Magnification hand arterigram from patient in Fig. 2. Note obliterations in the digital arteries.

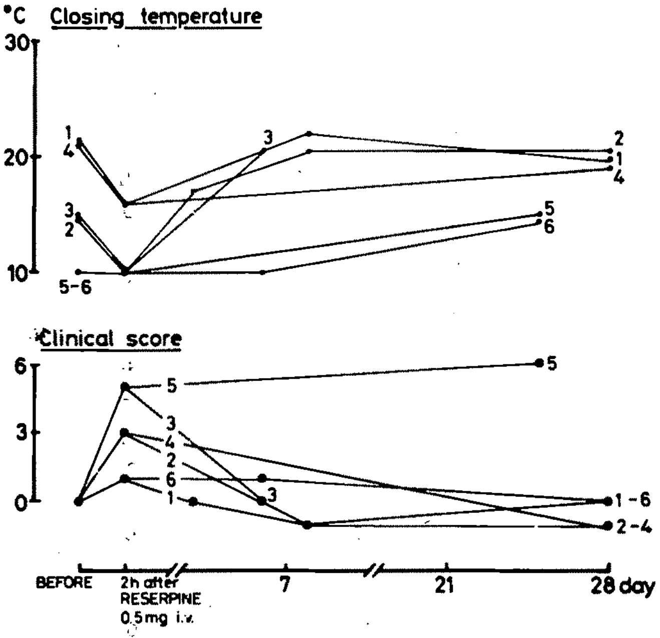


FIG. 4. Effect of reserpinisation in six patients with primary Raynaud's disease expressed as response to local cooling on closing temperature and the clinical score (Table 2).

the patients at room temperature will only benefit from injection of reserpine for less than a week by a lowered arterial tone.

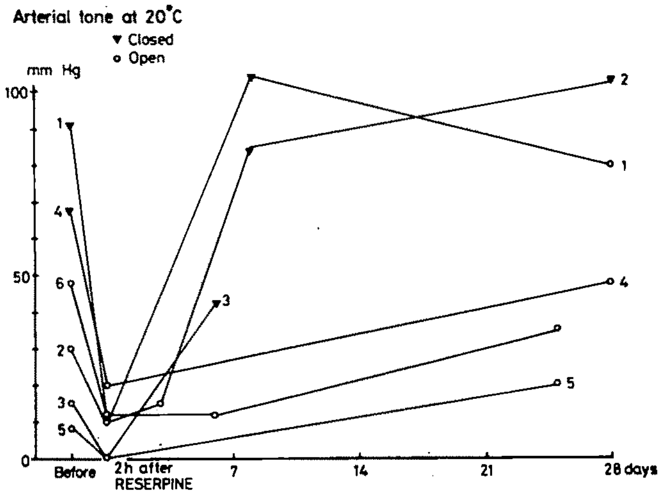


FIG. 5. Digital arterial tone estimated indirectly on fingers cooled to 20°C in six patients with primary Raynaud's disease, before and after reserpine injection.

Discussion

The presented measurements of the effect of reserpine on patients with Raynaud's disease have several important implications. The techniques used were hand arteriography and measurement of digital arterial tone during local cooling. The first method can demonstrate arterial obliterations, but as all contrast medias are more or less vasodilating, only measurements during local cooling can give clue to diagnosis of a 'vasospastic moment' in the disease. Measurements of digital arterial tone showed a decreased response of the digital arteries to local cooling for one to eight days after intraarterial injection of 0.5 mg reserpine with a maximum effect for one to two days. The objective measures followed closely the clinical effects registered by a score system, except in a patient showing sore healing.

There is ample evidence from animal experiments that the acute effects of intra-arterial reserpine administration is caused by a more or less complete and reversible depletion of sympathetic nerve endings for norepinephrine.[9] The norepinephrine release can initially give a pronounced vasoconstriction, but this is within some minutes to hours followed by a local vasodilatation with partial or complete absence of sympathetic tone and blocked response to sympathetic stimuli. The effects are maximal for one to two days and subside thereafter gradually eventually followed for a short period of hypersensitivity to norepinephrine and sympathetic stimulation. The generally held view that this time course is due to norepinephrine depletion of the sympathetic vesicles has been confirmed by histological studies on different tissues of the catecholamine stores.[9]

The time course for the action of reserpine resembles completely the clinical and experimental findings in the present study. This indicates that the direct pharmacological action of reserpine given as an intra-arterial injection is of short duration (from one to eight days). Reported effects of reserpine in Raynaud's disease vary both as to positive response and to duration of relief of symptoms. This could partly be explained by inhomogeneity of the patient materials because both primary and secondary forms of Raynaud's phenomenon are included. Long lasting effect of intraarterial reserpine for several months[1,12] seemed to be due to healing of ulcers and improvement of tender fingertips. The short term effects measured by changes in skin blood flow,[11] and on clinical parameters in a study with control injection in the opposite arm[5] had a duration of few days. The divergences are not incompatible, since sore healing only takes few days if circulation is improved shortly by the chemical sympathectomy caused by reserpine. If the sore fingertips are healed and then carefully protected they can be kept in a reasonably good condition for a long time. Such severe cases of Raynaud's disease might be the only indication for intra-arterial reserpine administration.

In a period with decreased response of the digital arteries to external cold attacks Raynaud's phenomenon will be less frequent and probably of shorter duration. If the hand temperature furthermore is elevated the cooling time necessary to reach the well defined closing temperature will be increased. Clinical observations are in agreement with these predictions.[1,5,11,12] However, the relatively short duration of the reserpine effect (one to eight days) reserves intra-arterial treatment with reserpine to the severe cases.[2] Not only is there a risk by repeated intra-arterial injections that should be given weekly, but reserpine has also been reported to be associated with development of breast cancer.

From the present study we conclude that the action of intra-arterial reserpine in humans corresponds to earlier findings in animal experiments. Beneficial effects for more than a few days are due to healing of ischemic lesions. Therefore therapy with reserpine should only be considered in severe cases of Raynaud's disease where amputation and sympathectomy might be postponed.

References

1. Abboud, F. M., Eckstein, J. W., Lawrence, M. S., et al.: Preliminary Observations on the Use of Intraarterial Reserpine in Raynaud's phenomenon. Circulation, 26:49, 1967.
2. Coffman, J. D., and Davies, W. D.: Vasospastic Diseases: A Review. Prog. Cardiovasc. Dis., 18:123, 1975.
3. Hirai, M., Nielsen, S. L. and Lassen, N. A.: Blood Pressure Measurements of all Five Fingers by Strain Gauge Plethysmography. Scand. J. Clin. Lab. Invest. 36:627, 1977.
4. Lewis, T.: Experiments Relating to Peripheral Mechanism Involved in Spasmodic Arrest of Circulation in Fingers, a Variety of Raynaud's Disease. Heart, 15:7, 1929.
5. McFadyen, I. D., Housley, E. and MacPherson, A. I. S. Intraarterial Reserpine Administration in Raynaud Syndrome Arch. Int. Med. 132:526, 1970.
6. Mendlowitz, M. and Naftchi, N.: The Digital Circulation in Raynaud's Disease. Am. J. Cardiol., 4:580, 1959.
7. Nielsen, S. L. and Lassen, N. A. Measurement of Digital Blood Pressure after Local Cooling. Submitted to J. Appl. Physiol.
8. Nielsen, S. L., Nobin, B. A., Hirai, M., et al.: Raynaud's Phenomenon Demonstrated by Local Cold Provocation. Submitted to Cardiovasc. Res.
9. Owman, C. and Sjøberg, N. O.: Difference in Rate of Depletion and Recovery of Noradrenaline in "Short" and "long" Sympathetic Nerves after Reserpine Treatment. Life Sci., 6:2549, 1967.
10. Porter, J. M., Snider, R. L., Bardana, E. J., et al.: The Diagnosis and Treatment of Raynaud's Phenomenon. Surgery, 77:11, 1975.
11. Romeo, S. G., Whalen, R. E. and Tindall, J. P.: Intraarterial Administration of Reserpine. Arch. Int. Med. 125: 825, 1970.
12. Willerson, J. T., Thompson, R. H., Hookman, P., et al.: Reserpine in Raynaud's Disease and Phenomenon. Short Term Response to Intraarterial Injection. Ann. Int. Med., 72:17, 1970.

Frozen Section Diagnosis of Breast Lesions

Recent Experience with 556 Consecutive Biopsies

PAUL PETER ROSEN, M.D.

From the Department of Pathology, Memorial Hospital, New York, New York

Experiences with frozen sections performed on 556 consecutive breast biopsies were reviewed. There were no false positive reports among the 145 (26%) lesions interpreted as carcinoma. Among 381 (68.6%) biopsies in which no carcinoma was found on frozen section, eight proved to contain carcinoma in other areas. Seven of the false negatives contained noninvasive carcinoma (six–*in situ* lobular; 1–intraductal). A small infiltrating lesion was found in the eighth case. The diagnosis was deferred to paraffin section in 30 (5.4%) of biopsies. Ten lesions proved to be noninvasive carcinoma and one was an infiltrating lobular carcinoma. Frozen section diagnosis is a highly reliable procedure for the diagnosis of infiltrating breast carcinoma. Noninvasive carcinoma may be overlooked at frozen section because of the limitations of sampling. Consequently, patients should be cautioned to await the paraffin section report if the frozen section does not reveal carcinoma. A frozen section diagnosis of carcinoma does not necessarily commit the surgeon to further surgery at that time and the information obtained from the frozen section may be helpful in beginning to plan further treatment with the patient.

THE FROZEN SECTION METHOD of diagnosis during surgery has proven to be highly reliable and as a consequence this procedure has proven exceedingly useful in the treatment of many diseases.[2,3,9] Recent criticism of the role of frozen section in the management of breast carcinoma[8] prompted us to review our current experience with the frozen section diagnosis of breast lesions.

Materials and Methods

In this laboratory, when a frozen section is reported to the surgeon, the diagnosis is also entered in a ledger kept in the frozen section area. All frozen section reports for 556 operative breast biopsies performed between October 1 and December 30, 1976 were reviewed. Material submitted as smears from aspiration biopsies was not included. The diagnoses given in these reports were then checked against the final diagnosis entered on the pathology report.

Diagnoses fell into three categories. Carcinoma was reported when it was clearly apparent. The diagnosis was deferred if microscopic findings raised concern about carcinoma, but were not considered to be definitive or if there were unusual clinical features to the case. The remainder of the specimens were reported as being benign. Multiple specimens were sometimes obtained from a single patient as biopsies of one or both breasts. The data presented refer to the number of specimens examined, not the number of patients.

Results

The initial frozen section reports described carcinoma in 145 or 26% of the specimens (Table 1). In some cases, the lesions were characterized as to specific type. All frozen section diagnoses of carcinoma were confirmed by examination of permanent sections.

The diagnosis was deferred for 30 or 5.4% of specimens. When this occurred, the specimen was processed as a "rush" so that a final report was usually available within 24 hours. Eight of the biopsies that involved a deferred diagnosis were performed for occult lesions detected by mammography. In six of these the histologic findings at frozen section were clearly benign but the diagnosis was deferred until more thorough sampling could be obtained because of concern raised by the mammogram. In the other two, the lesion had a worrisome microscopic pattern. No carcinoma was found in any of these eight specimens.

Hyperplasia or atypical hyperplasia of ducts or lobules was noted in 21 specimens and was the rea-

---

Reprint requests: Dr. Paul Peter Rosen, M.D., Department of Pathology, Memorial Hospital, 1275 York Avenue, New York, New York 10021.

Submitted for publication: March 26, 1977.

0003-4932-78-0100-0017-0060 © J.B. Lippincott Company

TABLE 1. *Results of Frozen Section in 556 Consecutive Breast Biopsies*

	# Biopsies	% Total Biopsies
Carcinoma	145	26.0
Benign*	381	68.6
Deferred†	30	5.4

* Eight of these specimens contained carcinoma after more extensive sampling by paraffin section.

† Eleven proved to be carcinoma on paraffin section.

son that the diagnosis was deferred. In ten cases, the lesion proved to be carcinoma when studied in paraffin sections. Six were lobular carcinoma *in situ* and four intraductal carcinoma. The other 11 biopsies proved to show varying degrees of hyperplasia.

A single biopsy that contained infiltrating carcinoma was also deferred. The lesion was an infiltrating lobular or small cell carcinoma in which there were relatively few tumor cells present. A second biopsy from the same tumor submitted for frozen section at the time of operation was considered to be diagnostic.

The final reports for the 381 or 68.6% of specimens described as benign were also reviewed. Carcinoma was found in eight when paraffin sections became available. These represented three per cent of the specimens reported to be benign at the time of frozen section and 1.4% of all breast biopsies submitted for frozen section during the period studied.

Review of the original frozen section slides and paraffin sections of the same tissue indicated that the frozen sections had been reported correctly as benign. In each case carcinoma was detected in a portion of the specimen other than the one selected for frozen section. Seven of the carcinomas were noninvasive (six–*in situ* lobular, one–intraductal). In one case an infiltrating duct carcinoma measuring 6mm in diameter had been missed on gross inspection. Six of these biopsies were from patients who had only one breast biopsied. In each case the indication for biopsy was a thickening or suspected mass. Five of these carcinomas were *in situ* lobular and one was the small infiltrating duct lesion.

Two patients had clinically apparent carcinoma of one breast. One woman was treated for simultaneous contralateral carcinoma and *in situ* lobular carcinoma was found in a routine biopsy of the opposite breast. The other patient had previously been treated for carcinoma of one breast and had an abnormal mammogram with focal calcification in the remaining breast. The area with calcification proved to be papillomatosis. Intraductal carcinoma was found in another part of the specimen.

Discussion

The results obtained in this review substantiate prior reports that documented the reliability of frozen section diagnosis for many types of specimens, including breast tissue.[1,3,7] In this series in which frozen section examinations were done by at least eight pathologists with varying years of experience in surgical pathology there were no false positives and the false negative rate was three per cent of those reported as benign. Recent criticisms of the use of frozen section for breast lesions have not questioned the accuracy of the method. Rather they have concentrated on the fact that surgeons may proceed with a mastectomy if a diagnosis of carcinoma is made by frozen section and that this deprives the patient of an opportunity to participate in decisions about the surgery to be performed. Obviously, the report obtained from a frozen section does not obligate a surgeon to perform any operation at that time. If it is agreed upon by the physician and patient, surgery could certainly be delayed in which case having the frozen section report would avoid waiting a day or more before the diagnosis would be available from routine sections.

One of the most important elements in maintaining the reliability of frozen section diagnosis of breast lesions, and especially for minimizing the frequency of false positive reports, is the option to defer a diagnosis to permanent section. In this series, diagnosis was delayed in 5.4% of biopsies, and nearly half of the lesions proved to be carcinoma. This group of cases included some of the most difficult breast lesions to interpret, namely those that called for making distinctions between duct and lobular hyperplasia or carcinoma. We have noted previously that papillomatosis is one of the lesions more commonly associated with mammographic abnormalities that lead to biopsy,[6] but this had usually not been the type of atypical proliferation that led to a deferred diagnosis. Similarly, in this series, most of the atypical lesions for which the diagnosis was deferred had *not* been detected by mammography. In most instances, it has not been a problem in histological interpretation that led to a deferred diagnosis when biopsies were performed for mammographic indications alone, but rather the presence of calcification in an area too large to be reliably sampled at frozen section or the feeling that such cases deserved more rapid processing even if the frozen section presented no serious problem in interpretation.

False negative reports constituted a smaller percentage of the total number of biopsies than deferred diagnosis. As might be expected, the lesions most likely to be overlooked or not appreciated on gross inspection of a biopsy were noninvasive carcinomas. This well recognized limitation of sampling is the reason that a patient must be cautioned by her surgeon to await the final paraffin section report even if the frozen section had been reported to be benign.

It has been suggested by one author[8] that another reason for avoiding the frozen section is to permit the pathologist an opportunity to assess the degree of malignancy by more thorough study of the tumor in paraffin sections. Oddly, this same author advocated the use of needle biopsy as a method equal to excisional biopsy for establishing the diagnosis of carcinoma. While either needle biopsy or aspiration[5] are valuable methods of diagnosis, neither permits a detailed evaluation of such prognostic morphologic factors as tumor grade, extent of lymphoid infiltration or the presence of vascular or lymphatic invasion.[4] Furthermore, failure to identify carcinoma in a noncystic mass by needle biopsy should be followed by excisional biopsy. Therefore, needle biopsy can only be considered to be a definitive procedure when it results in a diagnosis of carcinoma. This is most likely to occur with larger primary tumors that would presumably not be amenable to limited surgical treatment.

In the hands of competent pathologists the frozen section is one of the most accurate and reliable diagnostic procedures available. Experience is a particularly important ingredient in developing an awareness of when a diagnosis should be deferred and it is in this area that some of the most important judgements are made. At the risk of sometimes appearing overly cautious, however, it is best to defer the diagnosis when there is any uncertainty. A careful surgeon will be wise to agree to a deferred diagnosis if the pathologist expresses any concern about making a frozen section diagnosis rather than to push the pathologist into a decision.

Finally, it should be noted that although a frozen section diagnosis of carcinoma may make it possible for the surgeon to proceed with a mastectomy, this is not a necessary consequence of the frozen section method. In fact, the information obtained from the frozen section could well be used in discussing the available alternatives for further treatment should the diagnosis prove to be carcinoma.

References

1. Ackerman, L. V. and Ramirez, G. A.: The Indications For and Limitations of Frozen Section Diagnosis. Br. J. Surg., 46:336, 1959.
2. Horn, R. C., Jr.: What Can be Expected from the Surgical Pathologist from Frozen Section Examinations. Surg. Clin. North Am., 42:443, 1962.
3. Nakazawa, H., Rosen, P., Lane, N. and Lattes, R.: Frozen Section Experience in 3000 Cases. Am. J. Clin. Pathol. 49:41, 1968.
4. Nime, F. A., Rosen, PP., Thaler, H. T., et al.: Prognostic Significance of Tumor Emboli in Intramammary Lymphatics in Patients with Mammary Carcinoma. Am. J. Surg. Pathol., 1:25, 1977.
5. Rosen, P. P., Hajdu, S. I., Robbins, G and Foote, F. W., Jr.: Diagnosis of Carcinoma of the Breast by Aspiration Biopsy. Surg. Gynecol. Obstet., 134:837, 1972.
6. Rosen, P. P., Snyder, R. E. and Robbins, G.: Specimen Radiography for Non-palpable Breast Lesions Found by Mammography: Procedures and Results. Cancer, 34:2028, 1974.
7. Sparkman, R. S.: Reliability of Frozen Section in the Diagnosis of Breast Lesions. Ann. Surg., 155:924, 1962.
8. Webber, B. M.: Frozen Section—Frozen Attitudes. J. Surg. Oncol., 8:191, 1976.
9. Winship, T. and Rosvoll, R. V.: Frozen Sections. An Evaluation of 1,810 Cases. Surgery, 45:462, 1959.

Endoscopic Retrograde Cholangiography (ERC) in Surgical Emergencies

L. SAFRANY, N. VAN HUSEN, G. KAUTZ,* G. WITTRIN, M. CLEMENS,† R. WEITEMEYER‡

Twelve patients, presenting with an acute abdomen of suspected biliary tract origin, had endoscopic retrograde cholangiography performed. Eight patients had either traumatic, spontaneous, or postoperative biliary tract fistulas with five leading to the peritoneal cavity, one to the colon, one to the bronchial tree, and one to the liver parenchyma from a ruptured gall-bladder. Each was confirmed by endoscopic retrograde cholangiography. Four patients with jaundice, following traumatic rupture of the liver, had a pathological communication between the intrahepatic biliary tracts and the hepatic vascular system. It is concluded that ERC is a reliable method for obtaining precise localization of biliary tract problems in surgical emergencies both pre- and postoperatively.

From the Departments of Medicine and Surgery,
Westfälische Wilhelms University, Munster
West Germany and the Department of Surgery,
St. Joseph's Hospital, Hamilton, Canada

THE INDICATIONS FOR ELECTIVE endoscopic retrograde cholangiography (ERC) have become more clearly defined in the last few years.[6] However, in acute surgical emergencies involving the biliary tract, there are little data.[1,3–5] The patients in the present report illustrate a variety of problems in emergency biliary tract surgery during the course of 1870 ERCP examinations. Twelve patients are described who fulfill the surgical criteria of an acute abdomen with jaundice. Acute pancreatitis was excluded in each patient. ERCP was performed prior to operation in each patient.

Methods

Endoscopic retrograde cholangiography was performed in a manner previously described.[6,11] The ERC was accomplished within 15 minutes and was tolerated well even in patients with severe multiple trauma.

Results

The biliary tract was demonstrated in all patients, and the pancreatic duct was filled in five patients, and no untoward results were noted. The appropriate diagnoses are listed in Table 1.

Reports

Case 1. A 27-year-old female had increasing jaundice one week prior to admission (PTA). A cholecystectomy had been performed one year previously. She was septic and showed peritoneal signs of an acute abdomen. ERC showed the common bile duct and free flow of contrast media into the peritoneal cavity (Fig. 1).

Case 2. A 65-year-old male was admitted with right sided upper abdominal pain, absent bowel sounds, and jaundice. An incipient

---

* Medical Dept., Westfälische Wilhelms Universität, Münster, West Germany.

† Surgical Dept., Westfälische Wilhelms Universität, Münster, West Germany.

‡ Surgical Dept., St. Joseph's Hospital, MacMaster University Medical Centre, Hamilton, Canada.

Reprint requests: L. Safrany, Gastroenterologische Klinik, Reinhard-Nieter-Krankenhaus, 2940 Wilhelmshaven, West Germany.

Submitted for publication: March 12, 1977.

0003-4932-78-0100-0020-0060 © J.B. Lippincott Company

TABLE 1. *Patient Diagnosis*

Diagnosis	Number
Bilio-Peritoneal Fistula	5
Perforated Gallbladder	1
Bilio-Colonic Fistula	1
Bilio-Bronchial Fistula	1
Hepatic Cavitation (Rupture) with Bilio-Vascular Communication	4
	12

ileus was evident on a flat film of the abdomen. ERC (Figs. 2a, and b) demonstrated choledocholithiasis with a biliary fistula communicating freely between the gallbladder and the transverse colon.

Case 3. A 40-year-old female was admitted with septicemia six weeks after cholecystectomy. She had a chronic cough with bile-colored sputum. The assumed broncho-biliary fistula was localized with combined bronchography and retrograde cholangiography (Figs. 3a and b). The right lobe of liver communicated with the right lower lobe via a subphrenic abscess.

Case 4. A 17-year-old male was admitted following blunt abdominal trauma. During the next several days he became anemic and deeply jaundiced. Endoscopy confirmed bleeding from the ampulla of Vater. ERC showed a central cavitation of the right lobe of liver, the cause of the hemobilia and jaundice (Fig. 4).

Case 5. A 24-year-old male was admitted with increasing jaundice (bilirubin 23 mg) following blunt abdominal trauma. Previously the ruptured left lobe of liver had been surgically drained. ERC showed cavitation in the left lobe of liver with free flow of contrast into the inferior vena cava. The intraoperative cholangiogram is shown in Figure 5.

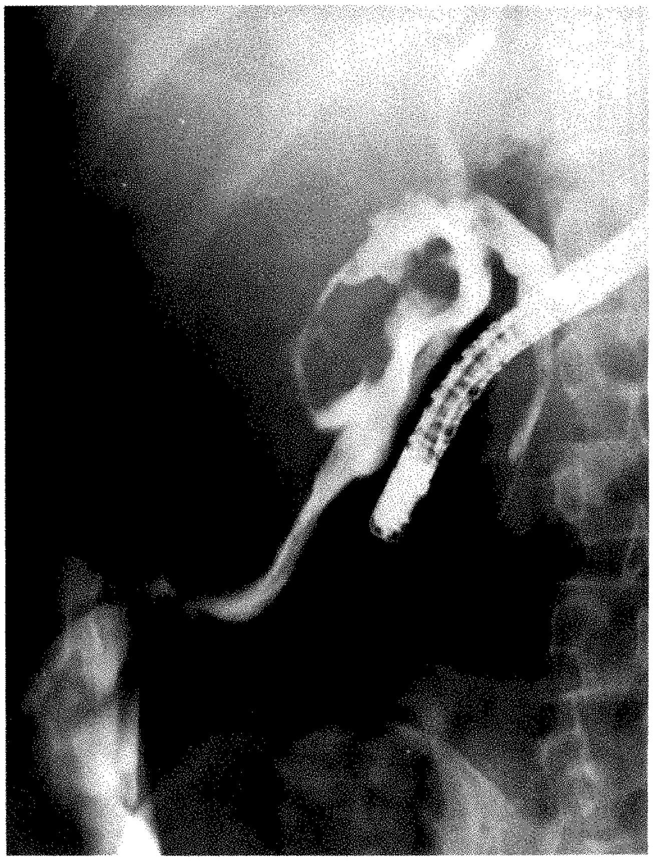
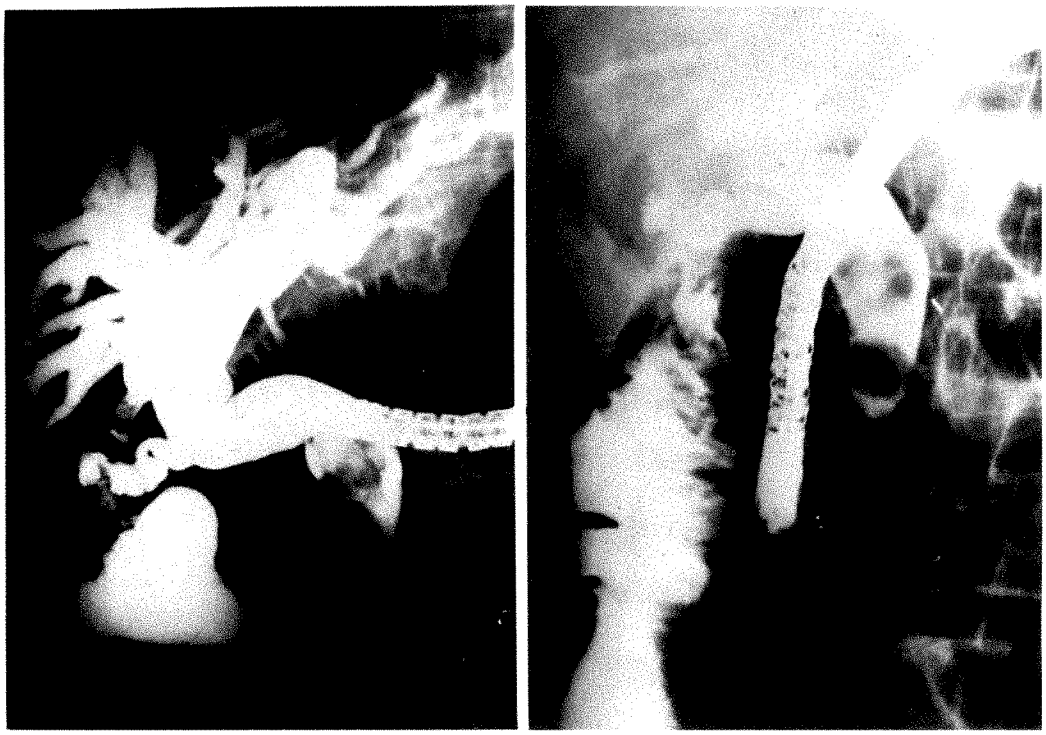


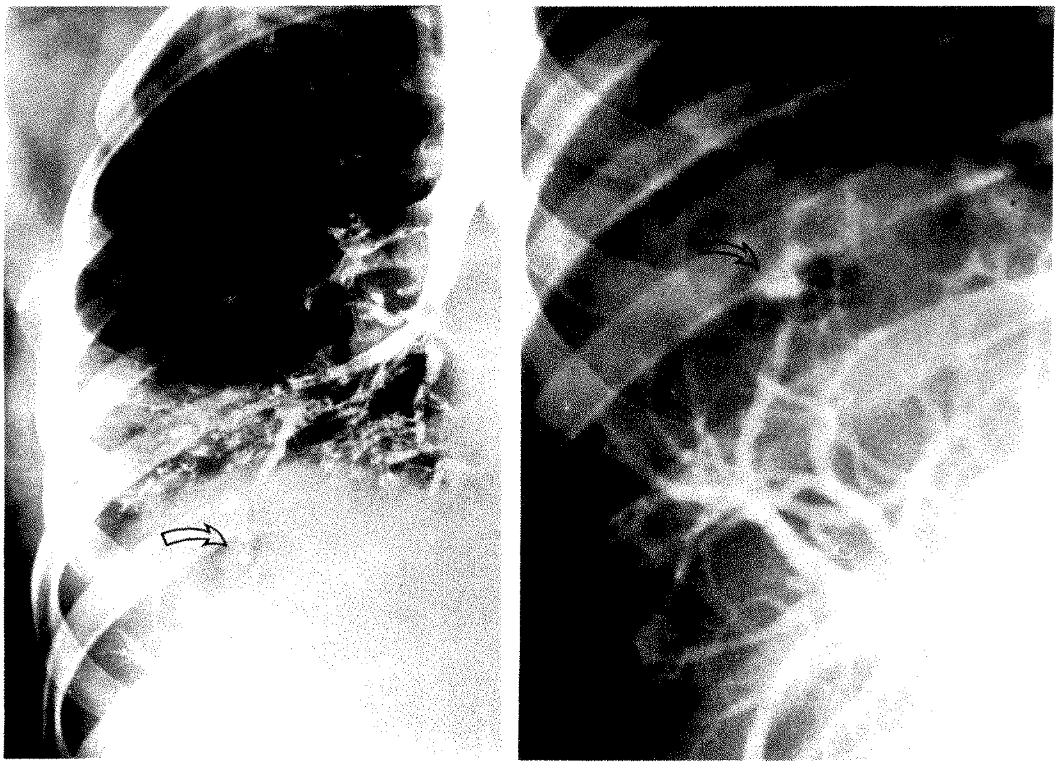
FIG. 1. The common bile duct is shown with free flow of contrast media into the peritoneal cavity.



FIGS. 2a and b. (a, left) Two stones are shown in a dilated common duct. (b, right) In a later phase, flow of contrast media from the gallbladder to the transverse colon is demonstrated.

P 24,762

UNIVERSITY COLLEGE OF MEDICINE LIBRARY



FIGS. 3a and b. (a, left) Simultaneous bronchogram and cholangiogram showing bronchobiliary fistula communicating via a subphrenic abscess. (b, right) Close-up view of communication and subphrenic abscess.

Case 6. A 57-year-old male was admitted twice in two months with severe pain in the epigastrium and left upper quadrant, which was associated with bilious vomiting. The temperature was 38.8°, with an elevated leukocyte count. Twice he was treated successfully with antibiotics. The upper gastrointestinal series and oral and intravenous cholangiogram were negative with a normal gallbladder. ERCP also showed a normal gallbladder, but as filling of the gallbladder continued, a sealed perforation into the liver parenchyma became apparent, and this was confirmed at operation (Fig. 6).

Discussion

Several methods are available to delineate the vascular and biliary anatomy of the liver. Initially, splenoportography was used to demonstrate a narrowed, obstructed or dilated venous segment.[17] Also, lesions within the liver were demonstrated by liver scan.[7] Liver biopsy, oral or intravenous cholangiography were of aid in only a few instances.[2,15] Operative cholangiography has been recommended by many.[7,10,13-15] The most successful and certain diagnostic method thus far as been selective hepatic angiography.[8,9,12] The above patients demonstrate that ERCP in emergency situations can be especially helpful. It allows the surgeon to anticipate a difficult situation.[13]

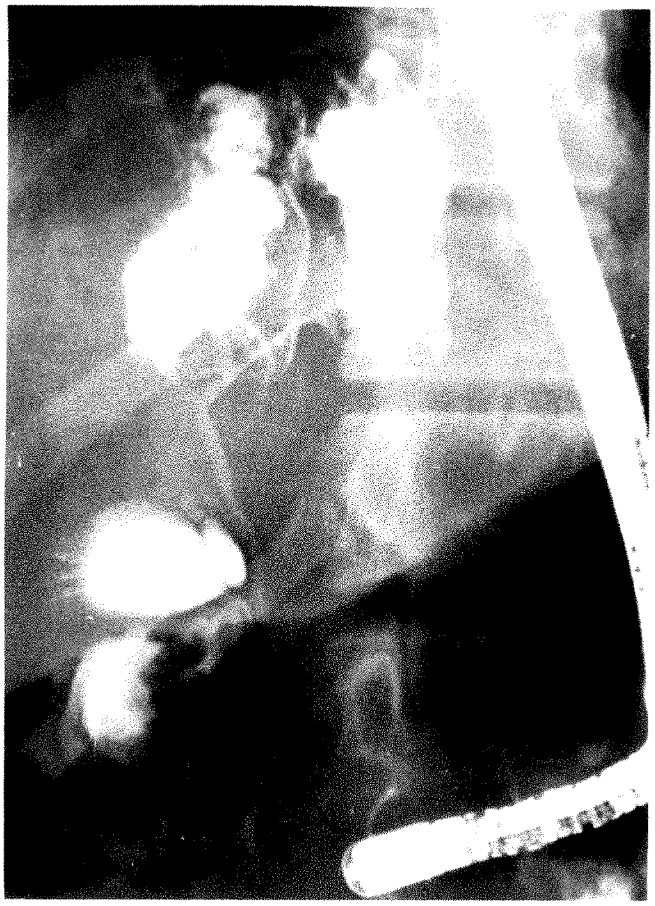


FIG. 4. Traumatic cavitation of the central portion of liver causing hemobilia.

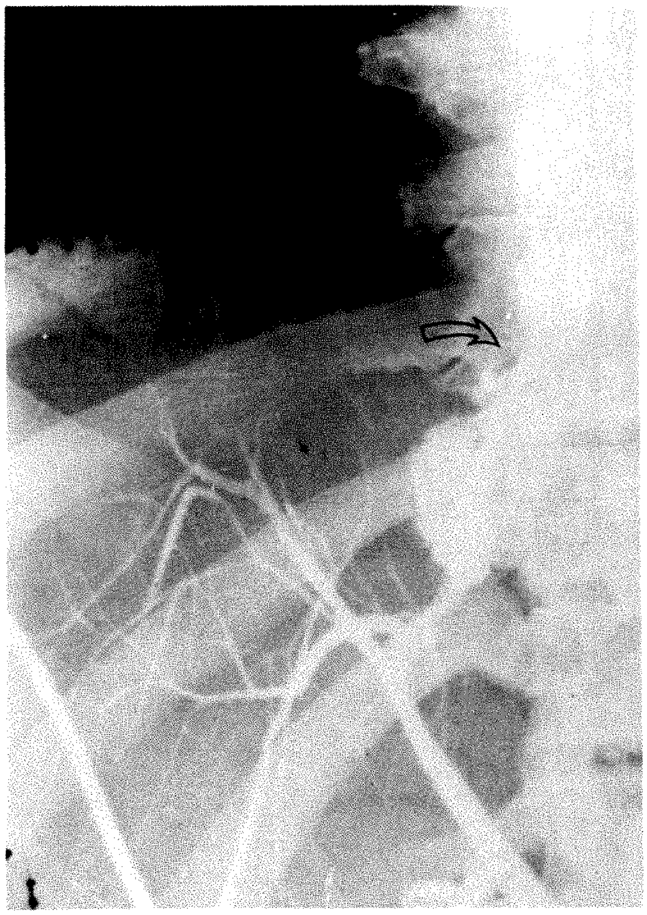


FIG. 5. Traumatic cavitation in the left lobe of liver is seen with free flow of contrast into inferior vena cava.

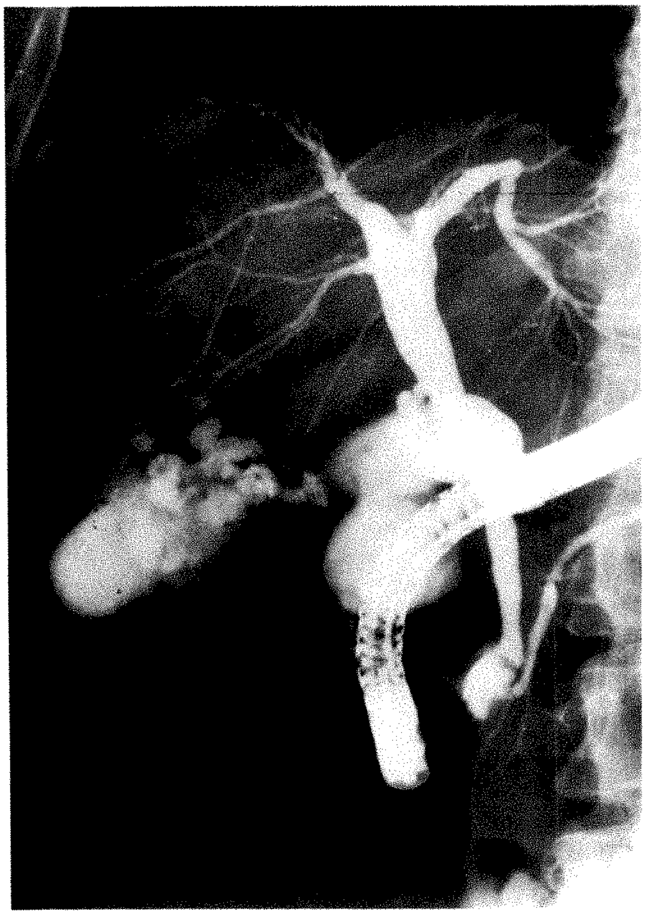


FIG. 6. Sealed gallbladder perforation penetrating into the liver parenchyma.

Hemobilia, broncho-biliary fistula,[16] bile peritonitis, bilemia, ruptured gallbladder all are cases where surgical intervention is indicated. ERC provides precise localization and a preoperative diagnosis.

References

1. Akovbiantz, A., et al.: Beitrag der Endoscopischen Retrograden Cholangiopancreatographie für die Chirurgie von Gallenweg- und Pancreaserkrankungen: Schweiz. Med. Wochenschr. 107:741, 1975.
2. Becker, H. D., Schaefer, H. E. and Peiper, H. J.: Posttraumatische Hämobile Infolge Arterio-biliäre Fisteln. Dtsch. Med. Wochenschr. 95:2316, 1970.
3. Blumgart, L. H., et al.: Endoscopy and retrograde choledochopancreatography in the diagnosis of the jaundiced patient. Lancet, 11:1264, 1972.
4. Classen, M., Frühmorgen, P., Kozu, T. and Demling, L.: Endoscopic Radiologic Demonstration of Bilio-digestive Fistulas. Endoscopy 3:138, 1971.
5. Clemens, M., Wittrin, G., Safrany, L. and Schönleben, K.: Die Bronchobiliäre Fistel. Chirug. 48:39, 1972.
6. Cotton, P.: Cannulation of the Papilla of Vater by ERCP. Gut, 13:1014, 1972.
7. Graff, R. J.: Considerations in the treatment of traumatic hemobilia. Am. J. Surg., 105:662, 1963.
8. Gunderson, A. E. and Green, R. M.: Traumatic Hemobilia: Accurate Pre-operative Diagnosis by Hepatic Artery Angiogram. Surgery 62:862, 1962.
9. Hendren, W. H., Warshaw, A. L., Fleischil, D. J. and Bartlett, M. K.: Traumatic Hemobilia: Non-operative Management with Healing Documented by Serial Angiography. Ann. Surg. 174:991, 1971.
10. Richter, J.: Zur Traumatischen Hemobilie. Zentralbl. Chir. 94:464, 1969.
11. Safrany, L., Tari, J., Barna, L. and Török, I.: Endoscopic Retrograde Cholangiography; Experience with 168 Examinations. Gastrointest. Endosc. 19:163, 1973.
12. Safrany, L., et al.: Die Hämobilie. Leber Magen Darm, 5: 229, 1975.
13. Sandblom, P.: Hemobilia. Surg. Clin. North Am. 53:1191, 1973.
14. Spencer, F. C., Menguy, R. and Eiseman, B.: Operative Cholangiography in the Management of Traumatic Hemobilia. Surgery 54:376, 1963.
15. Steichen, F. M. and Sheiner, N. M.: Traumatic Intrahepatic Hemobilia. Arch Surg. 92:838, 1966.
16. Watkins, L., et al.: Biliary-bronchial Fistula Demonstrated by ERCP. Can. Med. Assoc. J., 113:868, 1975.
17. Whelan, T. J. and Gillespie, J. T.: Treatment of Traumatic Hemobilia. Ann. Surg. 162:920, 1962.

Splenectomy in Myeloid Metaplasia

E. B. CABOT, M.D., M. F. BRENNAN, M.D.,* D. S. ROSENTHAL, M.D., R. E. WILSON, M.D.

A retrospective review of 19 patients with documented myeloid metaplasia undergoing elective splenectomy during the past ten years at the Peter Bent Brigham Hospital is presented. The primary indications for splenectomy in 17 of these 19 were either hypersplenism or symptomatic splenomegaly. Eighteen of the 19 underwent both ^{59}Fe-ferrokinetic studies and ^{51}Cr-sequestration studies or, alternatively, ^{111}In-marrow scintigraphy as a part of their routine preoperative evaluation. The death from sepsis of one patient six weeks postoperatively, whose marrow function was poor and whose level of splenic sequestration was minimal, confirms the efficacy of these studies in the preoperative prediction of hematologic response to splenectomy. Eighteen of the 19 patients benefited from the operation in terms of symptomatic relief and/or hematologic improvement, although surgery presumably did nothing to prolong survival in these patients. We conclude that splenectomy is indicated as a palliative maneuver for carefully selected patients with myeloid metaplasia without prohibitive operative risk, provided the criteria for selection of patients are adhered to and the surgeon and hematologist work together as a team.

From the Harvard Medical School, Department of Surgery, Peter Bent Brigham Hospital and Division of Hematology, Department of Medicine, Peter Bent Brigham Hospital, Boston, Massachusetts

THE ROLE OF SPLENECTOMY in the management of patients with myeloid metaplasia (MM) has continued to evoke controversy ever since this clinical entity became recognized within the spectrum of myeloproliferative disorders (MPD). The earliest literature on this subject generally reported a high operative mortality associated with little or no hematologic improvement. Hickling[8] in 1937 reviewed a total of 27 patients with myelofibrosis who had undergone splenectomy; 59% of the patients died. Similarly dismal reports dominated the literature on this subject for a number of years.[9,13,18] With a better understanding of the role of surgical intervention in this disease, improved results have been reported by a number of authors over the past 25 years.[1,3–5,10] In 1953 Green et al.[6] reviewed a total of 29 patients with MM, all of whom had undergone splenectomy, with an overall operative mortality (within a month after surgery) of ten per cent.

Recently, reports have appeared confirming the efficacy of splenectomy for specific indications in patients with MM, with diminishing operative mortality and improving clinical results.[11,14,15,17] Schwartz[16] has reported one operative death following elective splenectomy in a series of 21 patients with MM for a mortality of 4.8%. Among the survivors, he found significant symptomatic and/or hematologic improvement.

This report reviews our experience in 19 consecutive cases of known MM undergoing elective splenectomy at the Peter Bent Brigham Hospital (PBBH) since 1967, with an emphasis on the preoperative selection of patients, operative mortality, and postoperative clinical and laboratory results.

Materials and Methods

The hospital records of all patients treated at the PBBH between September, 1967 and November, 1976 with known MM and undergoing elective splenectomy were reviewed, retrospectively. Out of a total of 141 cases of MM diagnosed during this period, 19 patients underwent splenectomy, including 14 males and five females, and ranging in age from 38 to 72 (mean age 60.3).

The initial diagnosis of MM was made in the setting of splenomegaly on the basis of peripheral blood smear and bone marrow biopsy findings. Peripheral smears frequently showed tear drop formation and immature myeloid elements, often in the presence of elevated leucocyte alkaline phosphatase activity. Bone marrow biopsies were performed on all patients and showed varying degrees of myelofibrosis and atypical megakaryocytes. In all 19 patients who underwent

---

* Present address: c/o National Cancer Institute, Bethesda, Maryland.

Reprint requests: R. E. Wilson, M.D., Department of Surgery, Peter Bent Brigham Hospital, Boston, Massachusetts 02115.

Supported in part by N.I.H. Division of Research, Resources G.C.R.C. Branch, Grant No. RR00888.

Submitted for publication: January 31, 1977.

0003-4932-78-0100-0024-0085 © J.B. Lippincott Company

TABLE 1. *Primary Indications for Splenectomy in the 19 Study Patients*

Indications	Patients
Symptomatic splenomegaly	9
Hypersplenism	8
Possible splenic abscesses	1
Bleeding esophageal varices	1
Total	19

TABLE 2. *Comparison of Ferrokinetics and Red Cell Survival in 18 of the 19 Study Patients*

^{59}Fe Sacral Uptake	^{51}Cr Splenic Sequestration	Patients
present	+	8
present	−	4
decreased	+	5
decreased	−	1
Total		18

splenectomy, pathologic examination of the surgical specimens confirmed the presence of extramedullary hematopoiesis consistent with MM.

In all but three cases, operation was performed electively. One patient was thought to have multiple splenic abscesses making exploration more urgent. A second patient was operated on for bleeding esophageal varices and underwent splenorenal shunt for portal decompression in addition to splenectomy. The third patient required inferior vena caval interruption for recurrent pulmonary emboli in addition to splenectomy.

Data were accumulated on each of the 19 study cases with regard to management prior to surgery, indications for operation, certain aspects of operative technique, intra- and postoperative complications, pathologic findings, pre- and postoperative hematologic parameters, and eventual outcome.

Results

Indications for Splenectomy

Table 1 shows the breakdown of indications for splenectomy in the 19 study patients. Hypersplenism refers to thrombocytopenia and/or anemia with increasing transfusion requirements. All 19 patients had some degree of hypersplenism by the time they came to splenectomy, but this was the primary indication for surgery in only eight (42%). In nine patients (47%) the primary indication was symptomatic splenomegaly, including pain from capsular distension or splenic infarcts, abdominal fullness, or epigastric distress with early satiety. The patient thought to have a septic focus in the spleen had a long history of splenic pain and would doubtless have eventually come to splenectomy on the basis of symptoms alone.

In all cases, the patients had been followed by the Hematology Service at the PBBH before surgery. Prior to splenectomy, all but one patient were submitted to both ferrokinetic studies and red cell survival studies for splenic sequestration. Table 2 records the degree of ^{59}Fe sacral uptake, indicative of active marrow production of red cells, and ^{51}Cr red cell splenic sequestration, indicative of splenic destruction of red cells.[2] As stated by Button et al.,[2] a plot is made of the external splenic counts obtained for seven to ten days after an infusion of ^{51}Cr labeled erythrocytes. Significant splenic sequestration is implied by a slope ($\bar{m}$) greater than 150. On the basis of these studies, eight patients were classified as "ideal" candidates with splenic sequestration and good sacral marrow function. There were five patients, however, who showed splenic destruction of red cells but in whom sacral marrow production appeared decreased. These patients were considered to be marginal candidates based upon their hematologic indices, but other considerations prevailed. One patient, who had neither splenic sequestration nor good marrow uptake, failed to respond to splenectomy and died six weeks after operation.

Management Prior to Surgery

Table 3 summarizes the most common modalities of therapy employed for the 19 study patients at some point prior to splenectomy. In many patients more than one modality was used.

Four of the 19 had been diagnosed at an earlier time as having polycythemia vera, which later progressed to MM. Two of these required phlebotomy for control of polycythemia. Similarly, five patients received an alkylating agent for control of thrombocytosis during the proliferative phase of their disease.

In six patients, splenic irradiation had been used. Five of these six came to splenectomy primarily for symptomatic splenomegaly. Androgens were ad-

TABLE 3. *Use of Various Therapeutic Modalities in the 19 Study Patients Prior to Surgery*

Therapy	Patients
Splenic irradiation	6
Androgens	5
Alkylating agents	5
Corticosteroids	3
Transfusions alone	2
Phlebotomy	2
None	3

TABLE 4. *Operative Morbidity in the 19 Study Patients Following Splenectomy*

Complication	Patients
Bleeding	
Intra-operative (>4 units)	2
Requiring re-operation	2
Requiring postoperative transfusions	5
Pulmonary	
Pleural effusion	6
with atelectasis	5
with pneumonia	1
Other Infections	
Documented sepsis	1
Possible sepsis	1
Urinary tract infection	1
Stitch abscess	1
Cardiovascular	
Acute myocardial infarction	1
Possible (unproven) pulmonary emboli	3
Gastrointestinal	
Mild upper gastrointestinal bleeding	2
Prolonged ileus	1
Acute gastric dilatation	1

ministered to four patients and corticosteroids were given to two. One patient received courses of both androgens and corticosteroids.

Although most patients required transfusions at some point prior to surgery, only two patients were treated with transfusions alone. Three patients had no specific therapy prior to splenectomy.

Operative Technique and Morbidity

All operations were performed under general anesthesia. In the majority (16 patients), a left paramedian incision was used. The entire spleen and any accessory splenic tissue were removed in each case, and a liver biopsy was routinely performed for evaluation of the degree of extramedullary hematopoiesis. The spleens ranged in weight from 580–3500 g with a mean weight of 1700 g. In all 19 cases there was histologic confirmation of extramedullary hematopoiesis in the spleen, and usually in the liver as well.

Table 4 summarizes the operative morbidity for these 19 study patients. The total number of days for the hospitalization including their surgery ranged from eight to 51 days, with a mean of 23.3 days. However, the number of days in the hospital following splenectomy ranged from seven to 31, with a mean of only 13.6 days.

Deep drains left in the splenic fossa (three patients) were the exception rather than the rule; no patients developed documented subphrenic abscesses, and only two patients (both undrained) required reoperation for bleeding. These two patients had no further complications and were discharged from the hospital at 16 and ten days, respectively, after surgery.

There were no intraoperative complications that appeared to alter the immediate outcome. The patient with portal hypertension and bleeding esophageal varices required significant intraoperative blood transfusion (11 units); and several patients (seven others), including the patients who were reoperated on, continued to require varying amounts of blood (2–10 units total) for several days postoperatively. Two patients, one of whom was receiving anticoagulants for possible pulmonary emboli, developed minor gastrointestinal bleeding which resolved spontaneously in each instance without need for further transfusions.

The most common postoperative complication was left-sided pleural effusion (six patients) with atelectasis (five patients). Documented pneumonia occurred in only one patient (5.3%), and no patients required thoracentesis.

One patient had a superficial stitch abscess, but there were no other wound infections and no wound dehiscences. Patients were not routinely catheterized for surgery, and there was only one documented urinary tract infection (5.3%).

One patient who was mildly febrile postoperatively (no positive blood cultures), was investigated for a subphrenic abscess, but the fever responded to antibiotics without surgical intervention, and she was discharged from the hospital with antibiotic therapy eight days after splenectomy.

One 62-year-old, chronically ill patient ran a frankly septic course postoperatively and developed transient acute renal failure. The source of his sepsis was unknown at the time, and he was well enough to be discharged 17 days after surgery, only to be readmitted six weeks after surgery with sepsis secondary to a peri-rectal abscess, from which he did not recover. At autopsy he was also noted to have mild pancreatitis.

The most serious acute complication following splenectomy was that of a 69-year-old patient who suffered a cardiac arrest on the first postoperative day, secondary to an acute myocardial infarction with ventricular fibrillation. She made a full recovery, however, and was discharged on the twenty-seventh day after operation. This patient, as well as two others, was originally diagnosed as having a pulmonary embolism. However, in none of these patients was the diagnosis confirmed by angiography or by ventilation–perfusion lung scan, and they were not treated with long-term anticoagulants.

There were minimal gastrointestinal complications. One patient had prolonged ileus, in conjunction with pneumonia, requiring hospitalization for 24 days following surgery. One patient had an acute gastric dilitation, easily resolved by naso-gastric suction, and two patients had mild gastrointestinal bleeding, as mentioned above.

Hematologic Data

Platelet counts, hematocrits, and white blood counts (WBC) were obtained on the day prior to operation, one week postoperatively, and one month postoperatively. These data are presented in Figures 1–3. The ranges and means of each of these parameters at the three intervals are summarized in Table 5. The most noteworthy change was in the platelet count, which rose from a mean of 113,800/mm^3 preoperatively to a mean of 466,300/mm^3 at one week and 482,300/mm^3 at one month postoperatively. In three patients, the platelet count rose to greater than 1,000,000/mm^3. Although none of the nineteen study patients required platelet transfusions, six patients (32%) had preoperative platelet counts less than 50,000/mm^3. Only one patient had a platelet count below 50,000/mm^3 a month postoperatively; he was the patient who died of sepsis six weeks postoperatively.

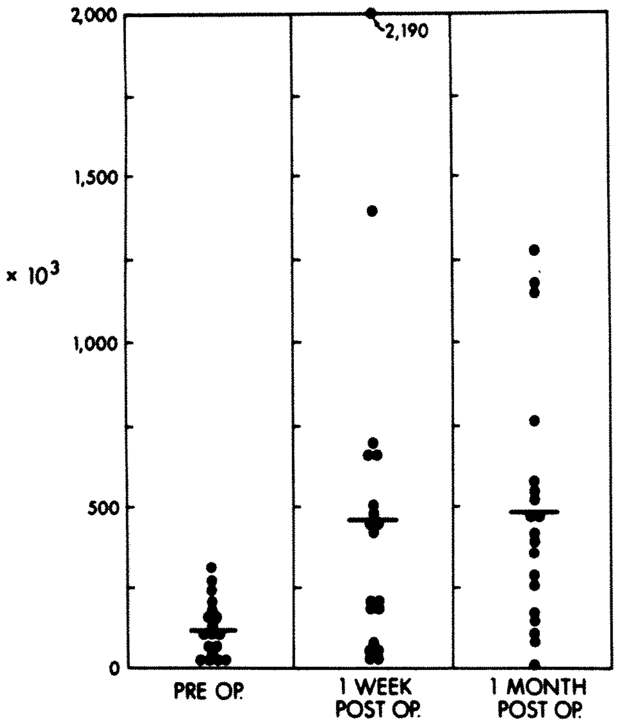


FIG. 1. Platelet counts and the associated means in the 19 study patients preoperatively, one week postoperatively, and one month postoperatively. The mean platelet count rose significantly ($p < 0.01$) one week following splenectomy and remained significantly elevated ($p < 0.001$) one month after surgery.

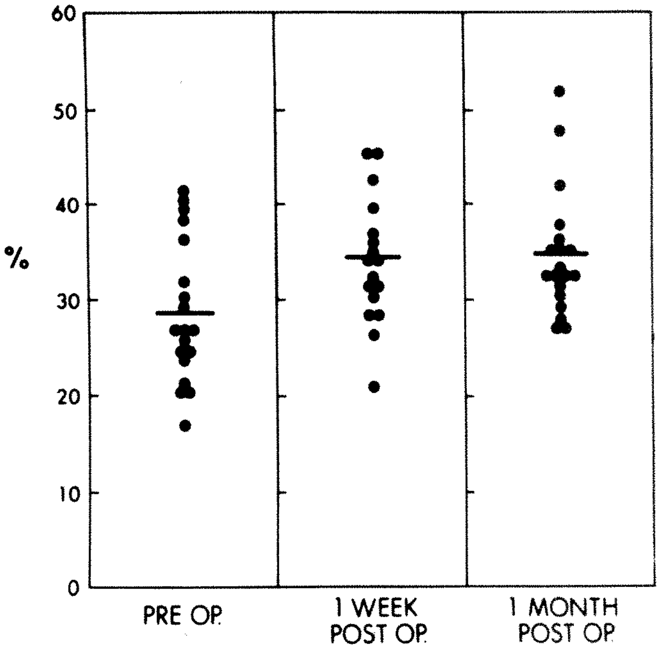


FIG. 2. Hematocrits and associated means in the 19 study patients preoperatively, one week postoperatively, and one month postoperatively. The significant rise in the mean hematocrit ($p = 0.042$) one week following splenectomy is a reflection of the fact that several patients were transfused postoperatively.

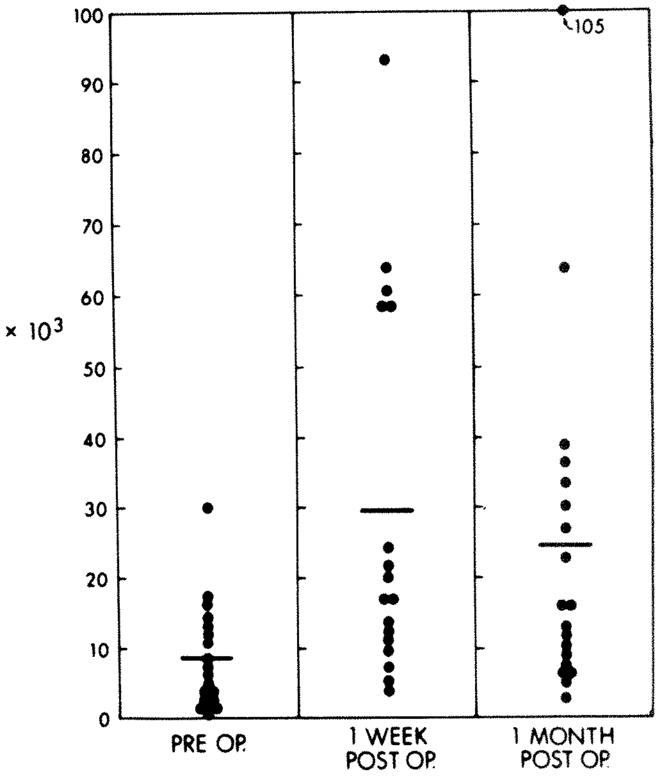


FIG. 3. White blood counts and associated means in the 19 study patients preoperatively, one week postoperatively and one month postoperatively. The rise in the mean WBC one week following splenectomy is statistically significant ($p = 0.002$).

TABLE 5. *Pre- and Postoperative Range and Mean of Major Hematologic Parameters in the 19 Study Patients*

	One day preop	One wk. postop	One mo. postop
Platelet Count ($\times 10^3$)			
range	23–300	23–2190	12–1270
mean	113.8	466.3	482.3
Hematocrit (%)			
range	17–41	26–45	27–51
mean	28.5	33.3	34.4
White Blood Count ($\times 10^3$)			
range	0.9–29.5	4.3–92.5	3.2–105.0
mean	8.6	29.3	24.4

Mortality

There were no intraoperative or immediate postoperative deaths. All 19 patients were discharged from the hospital following splenectomy (mean 13.6 days). Seven are alive from 13 to 73 months postoperatively with a mean followup of 44.7 months. These seven are comparatively well. Several require occasional transfusions, and one is troubled by recurrent pulmonary infections. The patient with portal hypertension and bleeding varices has a closed shunt but is alive four and one half years after operation and has not rebled.

Twelve of the 19 have died 1.5 to 39 months after surgery (mean 18.3 months). The earliest death occurred six weeks after operation in the patient with postoperative sepsis and acute renal failure, who was readmitted with a peri-rectal abscess and died of sepsis complicated by pancreatitis.

Four patients progressed to acute myelogenous leukemia, and all four have died five to 39 months after splenectomy (mean 19.8 months). Three patients are known to have developed presumably unrelated malignancies since surgery. Two of these have died of brain tumors, and the third tumor was a leiomyosarcoma discovered at autopsy in one of the patients who died of acute leukemia.

Two patients have died as a direct consequence of hemorrhages. One had an acute subdural hematoma following a head injury only 10 weeks after splenectomy, and the other died two and one half years later of retroperitoneal bleeding with no known antecedent trauma. Both patients were said to have had normal platelet counts within a week of their demise.

Of the remaining three deaths, one was due to a sudden myocardial infarction two and one half years after surgery, and one was due to endocarditis following open heart surgery for double valve replacement two and one half years after splenectomy. The third was a patient who died of pulmonary embolism and portal vein thrombosis eight months post-splenectomy, despite theoretically adequate control of his thrombocytosis with alkylating agents.

Discussion

Green et al.[6] concluded in 1953 that "splenectomy is not indicated in the majority of cases" since "most patients do not derive benefit from removal of the spleen." However, contrary to previous beliefs, they showed that "splenectomy does not often lead to failure of the blood forming system" and that "in certain carefully selected cases, the operation may be of definite therapeutic value." It has been known for many years that splenectomy does nothing to prolong survival in patients with MM, and that the risk of operation in these patients, more than any other in the spectrum of MPD, is quite high. This being the case, it is clear that strict criteria should be identified for the selection of patients for surgery, and that the risks of operation in these patients must be carefully weighed against the expected benefits.

Since 1967, all patients at our institution with postpolycythemia vera and agnogenic myeloid metaplasia have been studied by combined ferrokinetic and chromium survival studies[2] and, more recently, by ^{111}In marrow scintigraphy,[12] to determine residual marrow function and the degree of splenic sequestration. In the current series of patients, 18 of 19 patients had these studies performed, and on the basis of our retrospective analysis, 12 of these 18 patients would be considered to have enough residual active marrow hematopoiesis to compensate for the removal of splenic hematopoiesis (Table 2). Of the remaining six patients, the decision regarding splenectomy or other form of therapy had to be carefully weighed against the degree of splenic sequestration. Alternative modes of therapy for hypersplenism and splenic pain include the use of alkylating agents and/or splenic irradiation. Greenberger et al.[7] have recently reported on the results of cautious irradiation therapy in this group and found it to be, in selected patients, a safe and useful therapeutic alternative. The use of alkylating agents in the preoperative management of hypersplenism may seem paradoxical, but post-splenectomy thrombocytosis may be hazardous. In two patients, platelet counts rose to greater than 1,000,000/mm^3 and in one patient to over 2,000,000/mm^3. Preoperative therapy with alkylating agents has been aimed at keeping the platelet count near normal levels during the immediate postoperative course, hopefully to prevent thrombotic complications.

In reviewing our series of 19 patients with MM undergoing splenectomy, it appears that the criteria for operation were successfully applied in all but one case.

That is, 95% of our patients received at least some transient benefit from splenectomy in terms of either symptomatic relief or hematologic improvement or both.

In the case of the patient who died of sepsis six weeks post-splenectomy, this death must be considered as resulting from, or being in some way related to, the operative procedure. On the day prior to surgery, he had a platelet count of only 24,000/mm^3, with an hematocrit of 25.5% and a WBC of 3,300/mm^3. His ferrokinetic studies revealed poor marrow function, and red cell survival studies showed little splenic sequestration. These findings indicated that splenectomy could not be expected to improve this hematologic picture. He was operated upon, however, for symptomatic splenomegaly, rather than for pancytopenia. In the other 18 patients, the platelet count one month after splenectomy was significantly elevated over the respective preoperative value, the lowest being 86,000/mm^3 in a patient where the preoperative platelet count was 24,000/mm^3. In the patient who did poorly, however, the platelet count declined significantly from 24,000/mm^3 preoperatively to 12,000/mm^3 one month postoperatively, indicating a predictably poor hematologic response to splenectomy. The comparison of this patient's outcome with that of the other 17 patients who underwent ferrokinetic and red cell survival studies confirms the validity of these combined preoperative studies as important criteria in the selection of MM patients for splenectomy.

It should be pointed out, however, that the results of these studies, although useful in predicting the hematologic consequences of splenectomy, do not constitute the sole indication for operation. As previously noted (see Table 1), two patients, one with possible intra-abdominal sepsis and one with bleeding esophageal varices, required operation for potentially life-threatening complications of their primary disease. The fact that both had favorable hematologic outcomes following splenectomy is perhaps fortuitous. Of the nine patients with symptomatic splenomegaly as the primary indication for operation, one died of sepsis, as mentioned above, and the others were all relieved of their symptoms. Of the eight with hypersplenism as the primary indication, all had platelet counts above 80,000/mm^3 one month after splenectomy, and required significantly fewer transfusions than preoperatively.

The morbidity of splenectomy in our series of patients seems reasonably low (Table 4). There were relatively few infectious and hemorrhagic complications compared with previously reported series.[5,14,15,17] This undoubtedly reflects improving surgical techniques coupled with careful pre- and postoperative management and better patient selection. In the past, splenectomy for MM has been considered the one unequivocal indication for routinely leaving a deep drain in the splenic fossa, yet none of our 19 patients developed significant subphrenic collections, although only three were drained. On the other hand, the fact that two patients required reexploration for postoperative bleeding emphasizes the need for meticulous hemostasis under the left hemidiaphragm, where adhesions to the spleen frequently occur due to previous splenic infarcts.

The mortality from splenectomy in our series was also reassuringly low. Except for the patient who died of sepsis six weeks post-splenectomy, there were no deaths attributable to the operation itself, although the patient who died of pulmonary embolism and portal vein thrombosis eight months after surgery might possibly be considered a late death indirectly related to splenectomy.

Summary and Conclusions

A retrospective review of 19 patients with documented myeloid metaplasia undergoing elective splenectomy during the past ten years at the Peter Bent Brigham Hospital is presented. Their management prior to surgery, the indications for surgery, aspects of the surgical technique, their postoperative courses, the changes in hematologic parameters, and the eventual outcome for all 19 patients have been emphasized. Of the 19, there was only one early death and one late death possibly attributable to splenectomy.

Many authors in the past have pointed out the hazards of operation on patients with myeloproliferative disorders, particularly myeloid metaplasia. We wish to emphasize that prior to any consideration of elective surgery in such patients, they should be under the care of competent hematologists. Surgeon and hematologist must work together as a team with the full understanding that splenectomy may do nothing to prolong survival in MM. We believe, however, that in selected patients with evidence of marrow function and significant splenic sequestration, splenectomy can be successfully carried out with measurable, although transient, benefits to the patient in terms of symptomatic relief or greatly diminished transfusion requirements, or both.

References

1. Bouroncle, B. A. and Doan, C. A.: Myelofibrosis. Am. J. Med. Sci. 243:697, 1962.
2. Button, L. N., Rosenthal, D. S., Nathan, D. G., and Moloney, W. C.: Computer Evaluation of Ferro-Kinetic and ^{51}Cr Red Cell Survival, Volume and Sequestration in 37 Patients with

Myeloid Metaplasia. Abstracts International Society of Hematology, 15th Congress, 1974, p. 163.

3. Dameshek, W., Cartwright, G. E., Finch, C. A., et al.: Splenectomy in Myeloid Metaplasia with Myelosclerosis. Blood 10:550, 1955.
4. Fishman, N. and Ballinger, W. F.: Splenectomy. Arch. Surg. 90:240, 1965.
5. Gomes, M. R., Silverstein, M. N. and ReMine, W. H.: Splenectomy for Agnogenic Myeloid Metaplasia Surg. Gynecol. Obstet. 125:106, 1967.
6. Green, T. W., Conley, C. L., Ashburn, L. L. and Peters, H. R.: Splenectomy for Myeloid Metaplasia of the Spleen. N. Engl. J. Med. 248:215, 1953.
7. Greenberger, J. S., Rosenthal, D. S. and Moloney, W. C.: "Splenic Irradiation for Painful Splenomegaly in Myeloid Metaplasia: An Alternative to Splenectomy." Int. J. Rad. Onc. Biol. Phys. In Press.
8. Hickling, R. A.: Chronic Non-Leukemic Myelosis. Q. J. Med. N.S.G.: 253, 1937.
9. Jackson, H., Jr., Parker, F., Jr. and Lemon, H. M.: Agnogenic Myeloid Metaplasia of the Spleen. N. Engl. J. Med. 222:989, 1940.
10. Jensen, M. K.: Splenectomy in Myelofibrosis. Acta. Med. Scand. 175:533, 1964.
11. Laszlo, J.: Myeloproliferative Disorders (MPD): Myelofibrosis, Myelosclerosis, Extramedullary Hematopoiesis, Undifferentiated MPD, and Hemorrhagic Thrombocytopenia. Semin. Hematol. 12:409, 1974.
12. McNeil, B. J., Holman, B. L., Button, L. N. and Rosenthal, D. S.: Use of Indium Chloride Scintigraphy in Patients with Myelofibrosis. J. Nucl. Med. 15:647, 1974.
13. Reich, C. and Rumsey, W., Jr.: Agnogenic Myeloid Metaplasia of the Spleen. JAMA 118:1200, 1942.
14. Rosenthal, D. S. and Moloney, W. C.: Myeloid Metaplasia A study of 98 Cases. Postgrad. Med. March 1969, pp. 136–142.
15. Schwartz, S. I., Bernard, R. P., Adams, J. T. and Banman, A. W.: Splenectomy for Hematologic Disorders. Arch. Surg. 101:338, 1970.
16. Schwartz, S. I.: Myeloproliferative Disorders. Ann. Surg. 182: 464, 1975.
17. Silverstein, M. N. and ReMine, W. H.: Sex, Splenectomy and Myeloid Metaplasia. JAMA 227:424, 1974.
18. Wasserman, L. R. and Gilbert, H. S.: Polychthemia Vera and Myeloid Metaplasia. *In* Surgical Bleeding. Ulin, A. W. and Gollub, S. S., (ed.) New York, McGraw-Hill, 1966, p. 105–113.

"Current abstracts are amplified and illuminated by comments of the members of the Editorial Board, based on their own clinical experiences as well as those of other recognized authorities" . . . just one of the reasons why Lippincott's

Current Surgery *Formerly REVIEW OF SURGERY*

Editor: Lloyd M. Nyhus, M.D.

Associate Editors: Robert E. Condon, M.D.,
W. G. Schenk, Jr., M.D., Seymour Schwartz, M.D.

helps Resident (special rate only $15.00) and Veteran Surgeon alike to keep up with current progress, trends, and attitudes in all branches of surgery and the surgical specialties.

A true saver of precious reading time—from its detailed Contents Pages to its meaty reviews, and abstracts especially classified for reader convenience—a typical issue includes:

- Focus—several Reviews of timely or other special significance
- An original Report of major importance
- Twenty or more Abstracts with Commentary (and oft-times, rebuttal)
- Residents Corner—comprising Brief (1 to 3-page) Reports and Investigations
- In-depth Reviews of Current Books in Surgery

TO PUT THE BIMONTHLY REVIEW OF SURGERY AT YOUR FINGERTIPS NOW,

SUBSCRIBE TODAY . . .

J. B. LIPPINCOTT COMPANY, East Washington Square, Philadelphia, Pa. 19105 AS 1/78

Please enter my subscription to REVIEW OF SURGERY for 1 year (6 issues), at ☐ $19 (U.S.); ☐ $23 (all other countries); Resident Rate ☐ $15 (U.S. only; also note "year" of residency and Specialty ________).

PLEASE PRINT ☐ Payment Enclosed.

Name ________________ ☐ Charge my account.

Address ________________ My Specialty is:

City/State/Zip ________________ ________________

Notice to Contributors and Subscribers

Annals of Surgery is a monthly journal which considers for publication original articles in the field of surgery. It is the oldest continuously published journal in the English language solely devoted to the surgical sciences. The Editorial Board considers only papers judged to offer significant contributions to the advancement of surgical knowledge.

Contributions. Four typed copies of the manuscript and four copies of the illustrations should be sent prepaid to the Chairman of the Editorial Board of Annals of Surgery:

David C. Sabiston, Jr., M.D.
Annals of Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

Manuscripts and references should be typed double spaced on one side of 8½ × 11 paper leaving wide margins. Authors should retain a complete copy of the manuscript including illustrations in the event that the manuscripts are lost in the mail. A complete address for reprint requests should be included on the title page together with the name of the institution from which the work is being published.

An abstract of *not more than 200 words* should be placed at the beginning of the manuscript. It should accurately reflect the paper and provide readers with a reliable impression of the contents and conclusions of the work.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement should be expressed in the metric system. Temperature should be expressed in degrees centigrade. All contributions should be submitted in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Color illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink or transfer lettering, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

An alphabetical list of numbered references should appear at the end of the manuscript with corresponding numbers in the text. All references should be specifically mentioned in the body of the manuscript. The list of references should be *selective* with not more than 20 references except under unusual circumstances. References should conform to the style of the Index Medicus.

McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., 174:58, 1971.

PUBLISHER'S NOTICES

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

Business Address: Subscriptions, reprints, advertising, and all business communications should be addressed to:

Annals of Surgery
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $25.00 per year in United States and possessions; all other countries $34.00. All prices include postage. Single issues $4.00. Rate for Residents, U.S. only, $19.00.

The publishers accept no responsibility for opinions expressed by contributors.

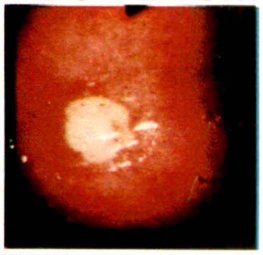
Olympus GIF-D3: when you must choose one fiberscope for diagnosis and therapy in all upper GI areas.

If there's a standard fiberscope for upper GI examination and electrosurgery, GIF-D3 is it. 200° maximum bending, 180° up and down and 100° left and right deflection mean easy insertion and a thorough diagnosis. There are virtually no blind spots in all areas from the esophagus to the descending limb. Therapeutic procedures are enhanced by the elimination of all exposed metal. A large selection of accessories helps you tailor GIF-D3 to your own procedure requirements. Find out more about the "Standard Upper GI Fiberscope," the ideal pan-endoscope. Write Olympus Corporation of America, 2 Nevada Drive, New Hyde Park, New York 11040.

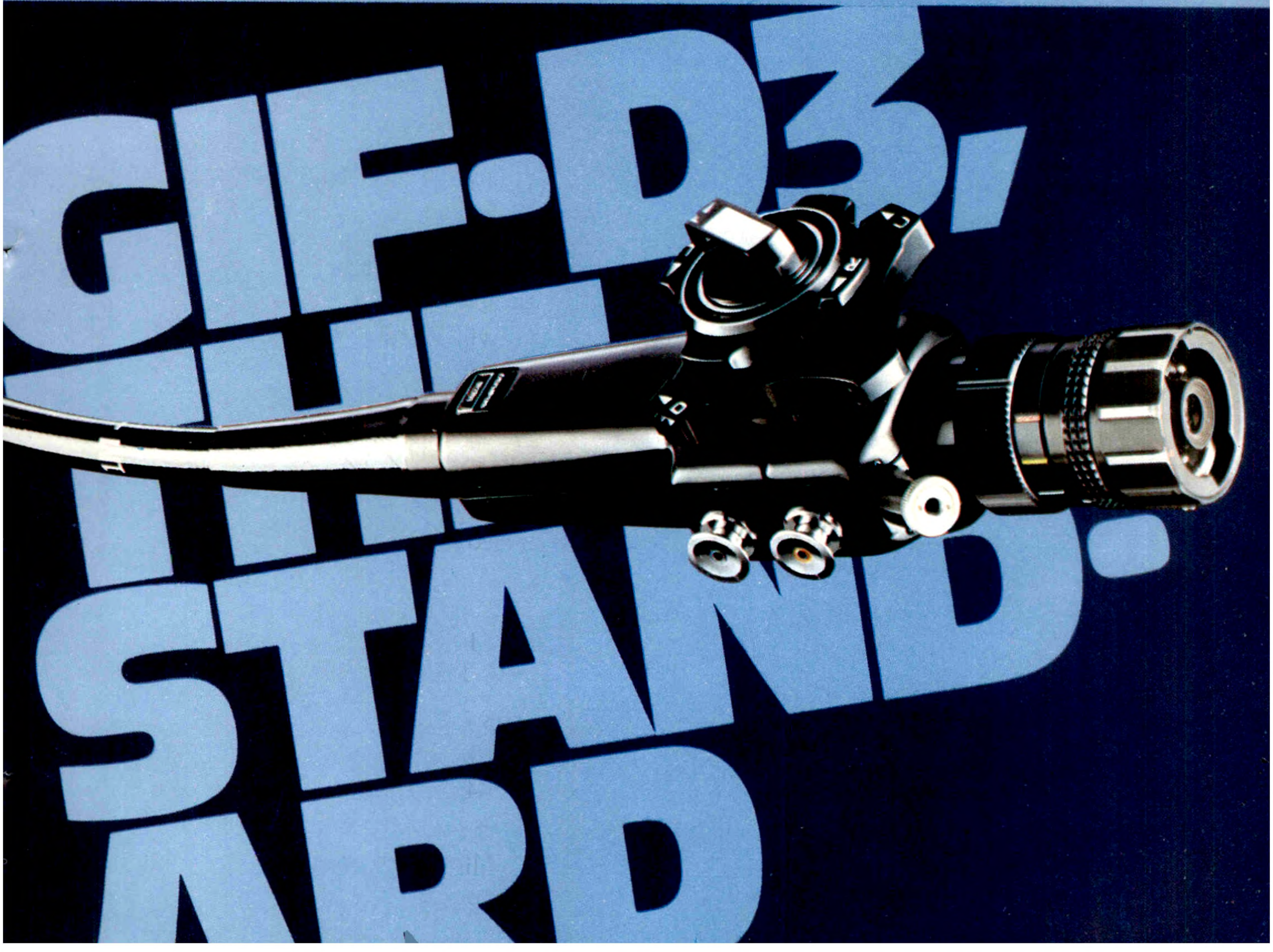
ESOPHAGUS

STOMACH

DUODENUM



OLYMPUS

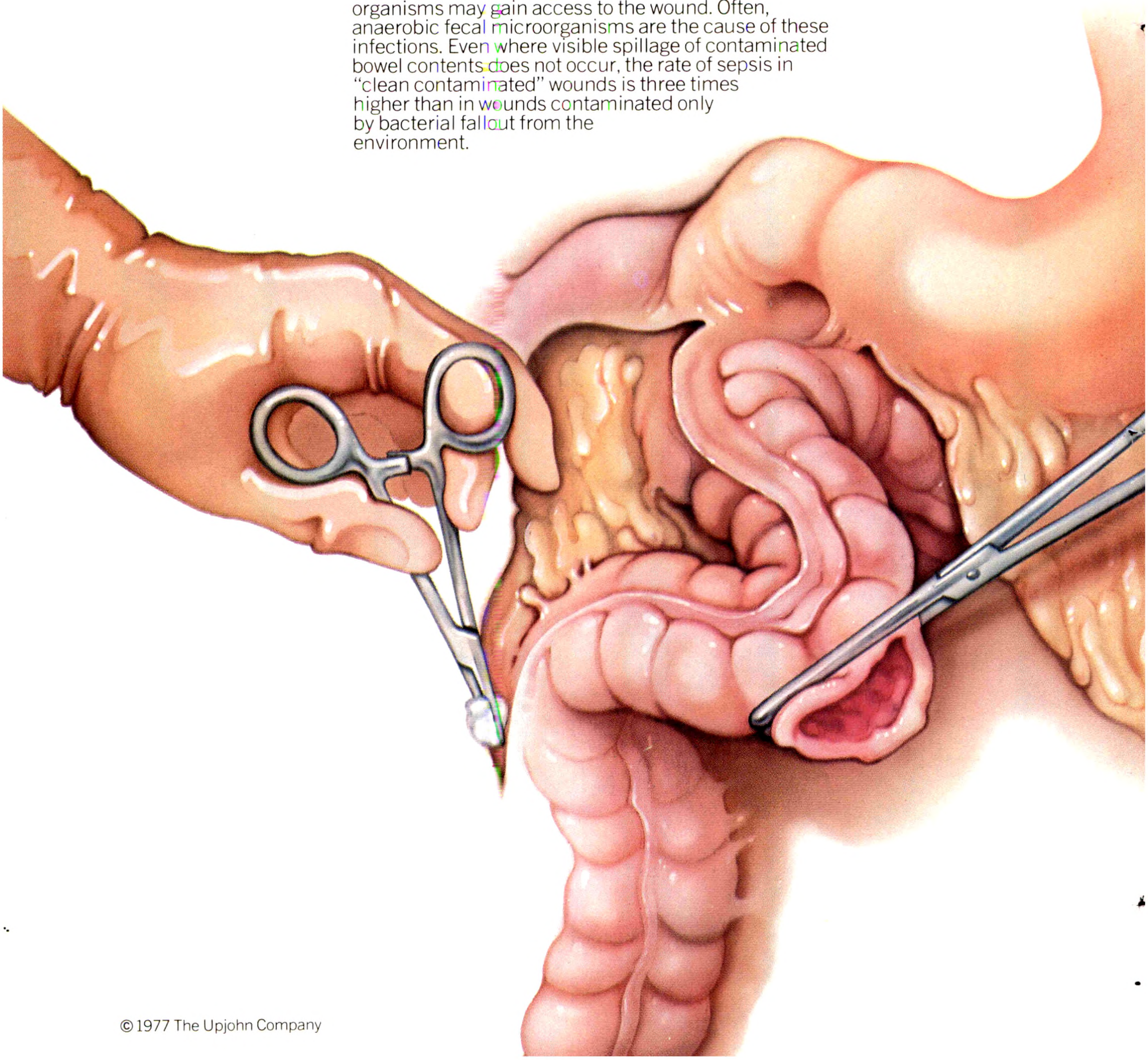


ANAEROBIC INTRA-ABDOMINAL INFECTIONS:

A MATTER OF MORBIDITY AND MORTALITY

Beware the breached bowel

Today, it is recognized that a majority of postoperative wound infections of the gastrointestinal tract are caused by contamination of the operative wound by endogenous organisms. When the bowel is opened by trauma, disease, or surgical manipulation, the organisms may gain access to the wound. Often, anaerobic fecal microorganisms are the cause of these infections. Even where visible spillage of contaminated bowel contents does not occur, the rate of sepsis in "clean contaminated" wounds is three times higher than in wounds contaminated only by bacterial fallout from the environment.



© 1977 The Upjohn Company

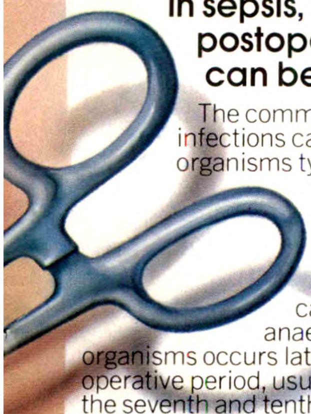
Summary Anaerobic fecal microorganisms are frequently implicated in the majority of postoperative abdominal wound infections. The major culprits are *Bacteroides fragilis,* clostridia species, and anaerobic cocci. Intra-abdominal anaerobic sepsis characterized by peritonitis and abscess formation usually starts between the seventh and tenth postoperative days. These intra-abdominal infections are associated with a particularly high incidence of morbidity resulting in hospitalization of patients for periods of 21 days to 80 days. As part of the total management of serious intra-abdominal infections, successful antibiotic therapy should incorporate antibiotics indicated and effective against the anaerobic as well as the aerobic pathogens that are present.

The anaerobic trilogy

In virtually all intra-abdominal infections, there is a recurring trilogy of anaerobes that are seen either singly or in combination, often mixed with aerobes.

This trilogy is composed of *Bacteroides fragilis,* clostridia species, and anaerobic cocci, particularly peptostreptococci and peptococci. In studies, *B. fragilis* has been isolated from 65% of intra-abdominal infections, clostridia in 60%, and anaerobic cocci in 32%.

In sepsis, the seventh postoperative day can be significant



The common wound infections caused by aerobic organisms typically develop clinical signs around the fifth to seventh postoperative day. Sepsis caused by anaerobic microorganisms occurs later in the postoperative period, usually between the seventh and tenth days. An intra-abdominal wound abscess that occurs weeks to several months postoperatively is almost always due to anaerobic microorganisms, often together with facultative bacteria.

Clinical evidence of infection important

The mere presence of aerobic or anaerobic bacteria in an operative incision is not synonymous with clinical infection. The differentiation between bacterial contamination and wound infection is a clinical decision. Evidence of wound sepsis includes wound tenderness that increases progressively in severity. Initially there is fever without spikes, but often spiking occurs in the afternoon or evening, returning to normal by morning. It is important to emphasize that a positive anaerobic culture without clinical signs is not an infection.

Clinical course of anaerobic infections

The first event in an anaerobic intra-abdominal infection is either generalized or localized peritonitis. If the patient survives early peritonitis, the usual progression is walling off of the infection, and abscess formation. These collections of pus can be located intraperitoneally, retroperitoneally, or within the viscera. Whether in the early peritonitis stage or in the later abscess stage, culture of purulent material yields anaerobes in the majority of cases. In fact,90% to 96% of intra-abdominal infections occurring with bowel perforation have been reported to be associated with anaerobic bacteria.

Unusually high incidence of morbidity and mortality

The highest incidence of anaerobic wound infection (usually *B. fragilis* and gram-negative organisms such as *E. coli* may both be isolated) follows resection of the large bowel — 10% to 15%. An infection rate of 5% to 10% may occur after surgical procedures involving the biliary tract and small intestine, whereas the rate following gastric or duodenal surgery is somewhat lower. It should be borne in mind that these infection rates are for elective operations. However, in emergency surgery for perforated appendicitis, diverticulitis, or traumatic wounds of the intestine, the infection rate can approach 40%.

Moreover, unusually long periods of morbidity are generally associated with intra-abdominal abscesses. Periods of hospitalization ranging from 21 days to 47 days for patients with intraperitoneal abscesses and 57 days to 80 days for patients with retroperitoneal abscesses have been reported. Mortality rates have been reported to range from 2% for patients with abscesses complicating acute appendicitis to 100% in patients with undrained hepatic, pancreatic, or retroperitoneal abscesses.

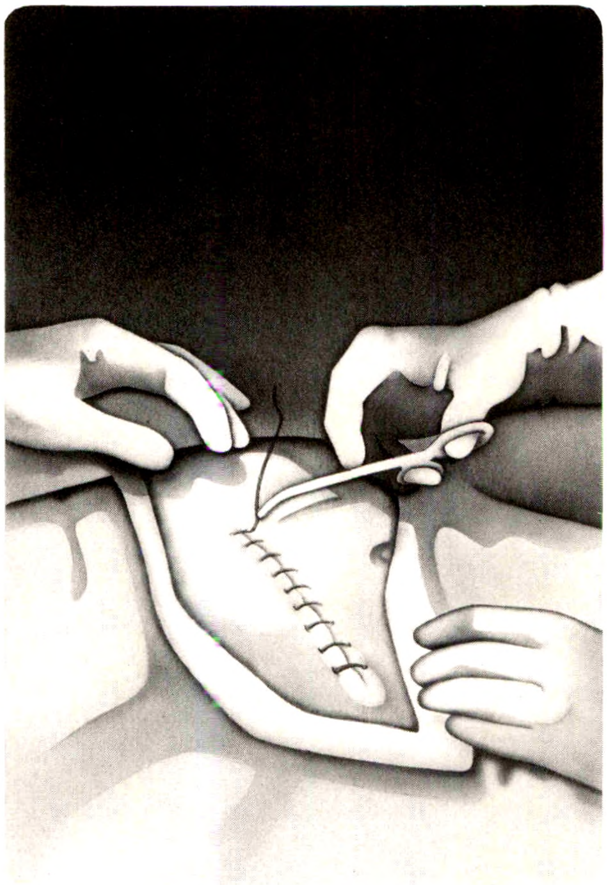
The role of antibiotics in therapy

Marked reduction in morbidity and mortality in anaerobic intra-abdominal infections is possible with earlier diagnosis, adequate surgical drainage, and proper choice of antibiotics. Successful use of antibiotics in infections complicating intestinal surgery involves knowledge of the probable organisms likely to be found in various clinical settings, the susceptibility of these organisms to antibiotics, and the risk of the infection to the patient in any given set of circumstances. In general, antibiotic therapy for serious intra-abdominal infections, whether in the acute phase or in the chronic abscess stage, should include drugs to manage anaerobic bacteria as well as facultative and aerobic organisms.

For information on one antibiotic to consider in treating serious intra-abdominal infections caused by infectious anaerobes, please turn the page.

Upjohn

Therapeutic considerations...



Anaerobic activity: Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection; serious lower respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; and serious skin and soft-tissue infections caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (e.g., erythromycin).

Indications include: serious lower respiratory tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances, the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions.

Other therapeutic considerations:

1. Cleocin PO_4 (clindamycin phosphate injection) is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Thus, Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section of the brief summary on the following page.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

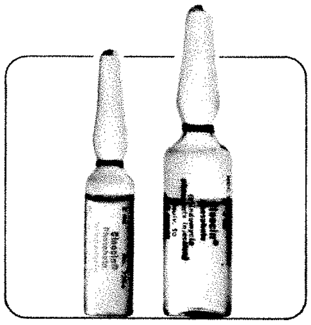
---

* Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g., *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)



CLEOCIN® PHOSPHATE (clindamycin phosphate injection) Sterile Solution – For Intramuscular and Intravenous Use.

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Hematopoietic: Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

J-5429-9 MED B-5-S

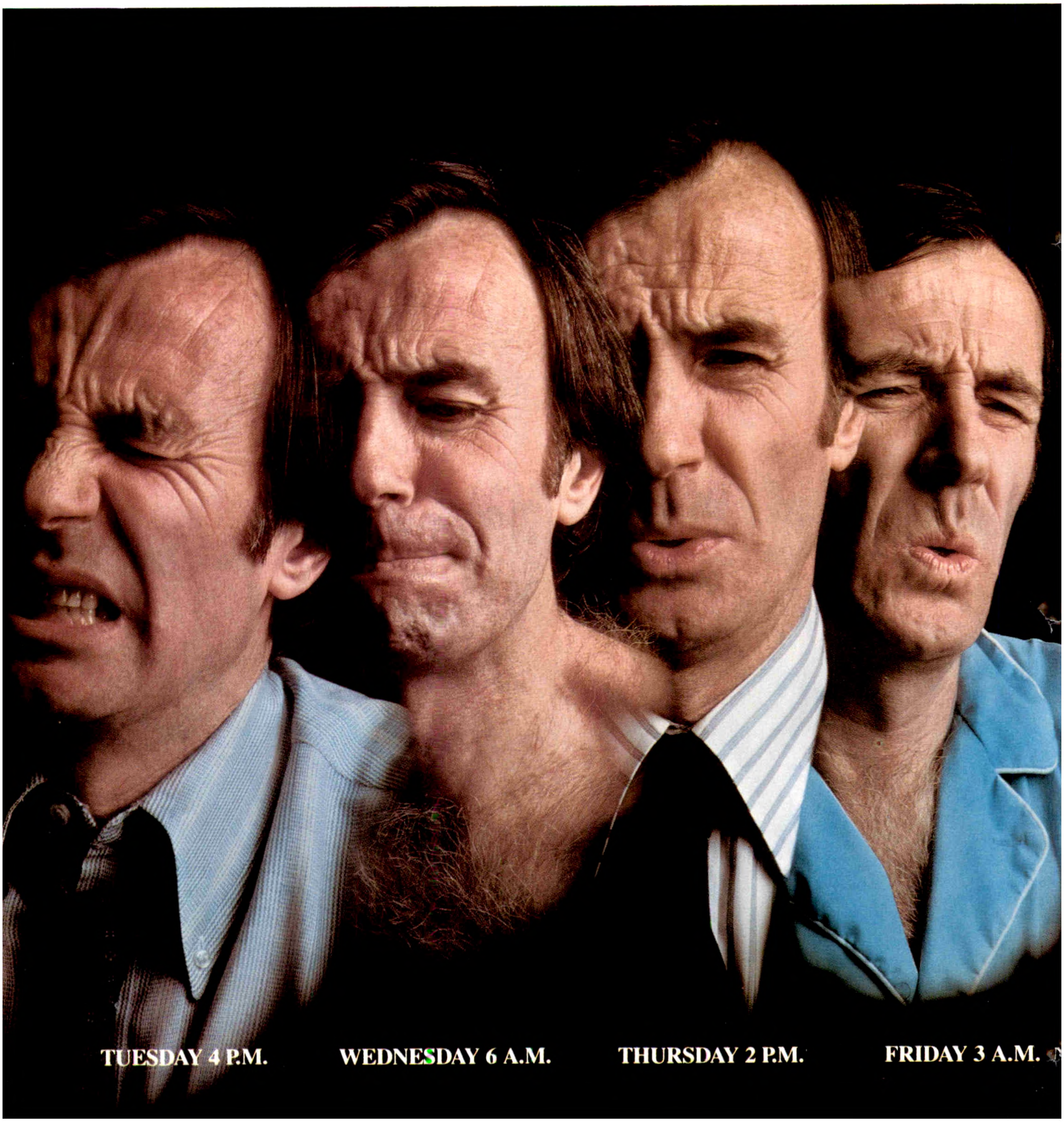
STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

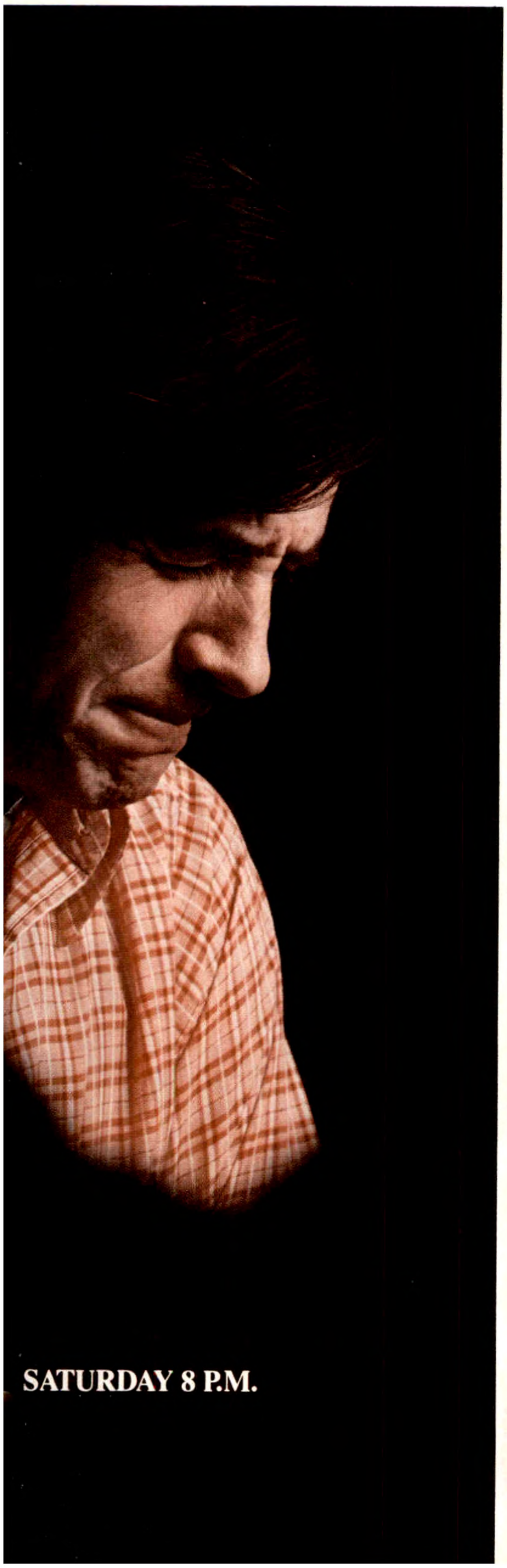
Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

PERSISTENT


TUESDAY 4 P.M.
WEDNESDAY 6 A.M.
THURSDAY 2 P.M.
FRIDAY 3 A.M.

PAIN It takes a special kind of analgesic to meet the need.

Talwin 50 mg. has what it takes:



SATURDAY 8 P.M.

Tolerance to its analgesic effect has been reported only rarely.

Potency in the codeine range – analgesia equivalent to 60 mg. codeine.

THE LOGICAL ALTERNATIVE TO OPIATES FOR RELIEF OF PERSISTENT PAIN OF MODERATE TO SEVERE INTENSITY

Talwin® HCl 50 mg.

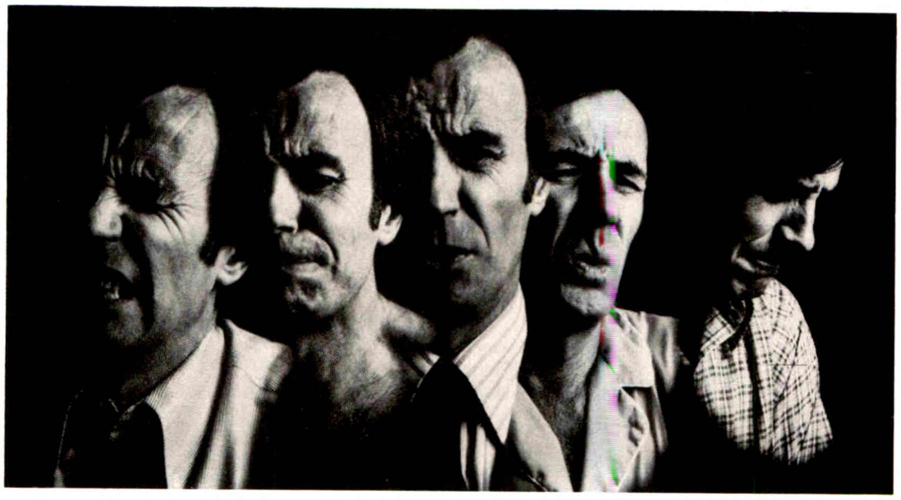
brand of

equivalent to 50 mg. base

pentazocine HCl tablets, NF

Winthrop

See next page for important product information including warnings, precautions, adverse reactions, and patient selection.



- Potency in the codeine range—analgesia equivalent to 60 mg. codeine
- A low risk of tolerance—has been reported only rarely
- Patients with chronic pain receiving Talwin 50 mg. for prolonged periods rarely experience withdrawal reactions when the drug is abruptly stopped: *There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally*
- Significant abnormalities of liver and kidney function have not been reported—even after extended use

Talwin® HCl 50 mg.

brand of pentazocine HCl tablets, NF
equivalent to 50 mg. base

THE LOGICAL ALTERNATIVE TO OPIATES FOR RELIEF OF PERSISTENT PAIN OF MODERATE TO SEVERE INTENSITY

Please consult full prescribing information before prescribing. A summary follows:

Talwin HCl is intended for the relief of moderate to severe pain. One 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. Talwin is a weak narcotic antagonist with sedative activity.

Contraindication

Hypersensitivity to pentazocine.

Warnings

Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin HCl should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations, disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions

Oral Talwin has been rarely reported to cause respiratory depression. It should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction, convulsive disorders and those about to undergo biliary surgery. As with all drugs, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

Adverse Reactions

Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations; and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, paresthesia, toxic epidermal necrolysis.

Dosage and Administration

Adults: The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg. Tolerance is rare. Abrupt discontinuance following chronic use has rarely caused withdrawal symptoms. Talwin is not subject to narcotic controls.

Overdosage

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

3011PPD

Albumin Uptake by Skin, Skeletal Muscle and Lung in Living and Dying Patients

PAUL C. SMITH, M.B., F.R.C.S., HOWARD A. FRANK, M.D., EARL J. KASDON, M.D.,
ELIZABETH C. DEARBORN, B.S., JOHN J. SKILLMAN, M.D.

Quantitative changes in albumin and water content which occur in skin and muscle tissue obtained by biopsy from clean surgical incisions at the time of skin incision and at the time of wound closure were assessed in seven patients who had major abdominal and vascular operations. Biopsies from skin, muscle and pulmonary tissue were obtained in a second group of nine patients who had thoracotomy for suspected bronchogenic carcinoma. The intravascular albumin mass decreased linearly with the duration of the operation ($r = 0.69$, $p < 0.01$) and was correlated significantly with a linear increase of extravascular albumin content in muscle ($r = 0.63$, $p < 0.01$). A significant increase of extravascular albumin occurred from the time of incision to the time of wound closure in the skin and muscle samples from both groups ($p < 0.05$–$p < 0.001$).

Extravascular albumin and water content were assessed in a third group of three postoperative patients who died with acute respiratory failure. Although the concentration of extravascular albumin in pulmonary tissue taken from this group was not different from the thoracotomy group, calculations based on the mean combined post mortem lung weights showed two to three times more extravascular albumin content. The histopathological findings are consistent with these changes. Thoracotomy was not associated with an abnormal increase in pulmonary extravascular albumin and water content, possibly because albumin does not gain access to the pulmonary extravascular space in increased amounts during operation in this clinical setting.

*From the Departments of Surgery and Pathology,
Harvard Medical School and the Beth Israel Hospital,
Boston, Massachusetts*

DEPLETION OF THE INTRAVASCULAR albumin mass following major operative procedures is recognized by surgeons as a common clinical abnormality.[8,14,16] Although wound edema, or an accumulation of fluid and protein into a third space induced by operative trauma, has been suggested as a partial explanation for this finding, the quantitative changes which occur at operative wound sites have not been clearly delineated.[12]

The present study was undertaken to assess the quantitative changes in albumin and water uptake by skin and muscle tissue at operative wound sites in two groups of patients, one of whom had a variety of general surgical and vascular procedures and the other of whom underwent thoracotomy for suspected bronchogenic carcinoma. Pulmonary tissue biopsies in the thoractomy group provide a basis to assess and to compare the changes in the postmortem pulmonary tissue of a third small group of three postoperative patients who died with acute respiratory failure. These data allow inferences to be made concerning the distribution and effect of albumin infusion on postoperative respiratory function.

Materials and Methods

Sixteen patients undergoing a variety of general and vascular (group 1, $n = 7$) and thoracic (group 2, $n = 9$) operative procedures were studied (Table 1). Patients in group 2 underwent thoracotomy for suspected bronchogenic carcinoma.

Biopsies of skin and muscle were taken from the operative wound site at the time of incision and again at the time of wound closure in both groups (Table 2). Lung biopsies were taken from the lobe to be resected when the chest was opened and again just before the lobe was removed (Table 2). In patient 12, the second biopsy was taken from unresected, normal lung. In another patient (patient 16), resection of lung was not possible. Skin and muscle biopsies, only, were available for analysis in this patient. All patients were given inhalation anesthesia with a 50% mixture of nitrous oxide and oxygen, supplemented with curare and morphine. A standard single lumen endotracheal tube was used in all patients. The lung to be resected was partially ventilated throughout operation.

Preoperative plasma volumes were measured with

Reprint requests: John J. Skillman, M.D., Department of Surgery, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

A portion of this work was abstracted and published in Surg. Forum 26:91, 1975.

Submitted for publication February 4, 1977.

0003-4932-78-0100-0031-0085 © J.B. Lippincott Company

TABLE 1. *Clinical Data of 16 Patients Studied*

Patient/Group	Age years	Sex	Operative Procedure	Duration of Operation hours
General and Vascular				
1	19	M	Bilateral nephrectomy	3.5
2	66	M	Incisional & inguinal hernioplasties	5.0
3	66	F	Colon resection	5.0
4	58	F	Abdominal aneurysmectomy	5.0
5	74	M	Colon resection	6.5
6	71	M	Abdominal aneurysmectomy	9.0
7	38	F	Left hepatic lobectomy	10.0
Mean ± SEM	56 ± 8			6.3 ± 0.9
Thoracic				
8	73	F	Left upper lobectomy	7.5
9	70	M	Left upper lobectomy	8.5
10	60	M	Right upper lobectomy	5.0
11	86	M	Right upper lobectomy	8.5
12	55	M	Right middle lobectomy	5.0
13	65	F	Left pneumonectomy	7.0
14	46	M	Left pneumonectomy	5.0
15	57	M	Thoracotomy	6.5
16	68	M	Thoracotomy	6.5
Mean ± SEM	64 ± 4			6.6 ± 0.5

Evans blue within the 24 hour period before operation and immediately after operation in the recovery room in all 16 patients (Table 3). Total protein was measured by the Biuret method.[18] Serum albumin concentration was measured by electrophoresis with cellulose acetate strips. Serum oncotic pressure,[7] hemoglobin and hematocrit were also measured before and after operation. The circulating albumin mass was calculated as the product of plasma volume and serum albumin concentration and was corrected for albumin infused during operation. Five patients in group 1 and eight patients in group 2 received infusions of albumin during the operative procedure (Table 3).

Postmortem lung biopsy samples for tissue analysis and histology were studied in three patients who died in acute respiratory failure (Table 4). Samples were taken from both superior and inferior (dependent) portions of the three right lung lobes and two left lung lobes to avoid artifact due to gravity. These samples were compared with the lung biopsy samples from the patients undergoing thoracotomy (Table 5).

Freshly cut biopsy specimens measured approximately 2.5 × 1.0 × 1.0 cm for skin, 1.5 × 1.0 × 1.0 cm for muscle and 1.5 × 1.5 × 1.5 cm for lung. Muscle biopsies were taken from the rectus abdominis muscle in patients in group 1 and from the latissimus dorsi muscle in patients in group 2. All biopsy specimens were placed immediately in aluminum containers with moisture tight covers and frozen on powdered dry ice. Specimens were trimmed while frozen to give central

TABLE 2. *Total and Extravascular Albumin Measurements and Water Content of Tissue Samples from 16 Patients Studied*

Measurement	General and Vascular				Thoracic						Combined Groups			
	Skin		Muscle		Skin		Muscle		Lung		Skin		Muscle	
	B_1	B_2	B_1	B_2	B_1	B_2	B_1	B_2	B_1	B_2	B_1	B_2	B_1	B_2
Total Albumin mg/g fat free wet tissue	8.2 ± 0.6	9.0 ± 0.7	3.8 ± 0.5	5.4 ± 0.8	8.6 ± 0.6	10.7 ± 0.9	4.0 ± 0.4	5.1 ± 0.4	12.5 ± 1.0	13.0 ± 1.5	8.4 ± 0.4	9.9 ± 0.6	3.9 ± 0.3	5.3 ± 0.4
p Values	<0.025		<0.025		<0.005		<0.005		NS		<0.001		<0.001	
Extravascular albumin mg/g fat free wet tissue	7.4 ± 0.7	8.5 ± 0.7	1.4 ± 0.3	3.5 ± 0.7	8.0 ± 0.7	10.1 ± 0.9	2.4 ± 0.3	3.5 ± 0.4	9.6 ± 0.8	8.7 ± 1.4	7.7 ± 0.5	9.3 ± 0.6	2.0 ± 0.3	3.5 ± 0.4
p Values	<0.001		<0.005		<0.025		<0.05		NS		<0.001		<0.001	
Water Content %	69.3 ± 2.3	72.6 ± 1.3	77.7 ± 1.8	82.1 ± 1.9	71.9 ± 2.0	71.6 ± 3.8	82.0 ± 1.0	84.9 ± 1.1	83.4 ± 1.4	80.0 ± 1.8	70.6 ± 1.5	72.1 ± 1.9	80.1 ± 1.1	83.7 ± 1.0
p Values	NS		<0.05		NS		<0.025		<0.05		NS		<0.025	

All values are mean ± SEM. p Values = paired t test comparing B_1 and B_2 values; NS = not significant. B_1 = First biopsy; B_2 = second biopsy

TABLE 3. *Plasma Volume, Albumin Concentration, Circulating Albumin Mass, Serum Oncotic Pressure, and Albumin Infused in two Groups*

	Group					
	General & Vascular		Thoracic		Combined Groups	
Measurement	preop	postop	preop	postop	preop	postop
Plasma volume (ml)	3251 ± 279	2695 ± 116	3079 ± 302	2892 ± 337	3154 ± 204	2806 ± 193
p Value	NS		NS		<0.025	
Serum Albumin (g/dl)	3.4 ± 0.2	3.3 ± 0.1	3.3 ± 0.2	3.4 ± 0.2	3.4 ± 0.1	3.4 ± 0.1
p Value	NS		NS		NS	
Circulating albumin mass (g)	135 ± 9	89 ± 5	132 ± 17	98 ± 11	133 ± 10	94 ± 7
p Value	<0.005		<0.005		<0.001	
Serum Oncotic Pressure (mm Hg)	25 ± 1.1	23.5 ± 1.3	25.1 ± 1.0	24.1 ± 1.2	25.0 ± 0.7	23.8 ± 1.8
p Value	NS		NS		NS	
Albumin infused during operation (g)	23 ± 10		33 ± 10		28 ± 7	

All values are mean ± SEM. p values = paired t test. NS = not significant

portions weighing 0.3 to 0.5 g. The central portions were weighed in preweighed aluminum containers and the samples were diluted 20 fold (W/V) with 0.9% saline containing 0.1% sodium deoxycholate. Each sample was homogenized in the cold. An aliquot (0.5 ml) of homogenate was taken for determination of water and fat content by the method of Flear et al.[4] The remainder was centrifuged at 1800 r.p.m. for 20 minutes and then at 30,000 g for a further 20 minutes. The supernatant fluid was divided into two portions, each of which was frozen for determination of total albumin and hemoglobin content.

Total albumin content of the supernatant fluid was determined with radial immunodiffusion plates (Hyland Laboratories).[11] Extravascular albumin content[9] was determined as the difference between total and intravascular albumin content, the latter being the albumin which was contained in the blood trapped in the tissue samples. Intravascular albumin content was calculated from blood contained in the supernatant fluid by the following calculations:

1. mg albumin/g fat free wet tissue

$$= [\text{ml plasma/g tissue}] \times [10^{*}\,(\text{g albumin/100 ml plasma})] \times \frac{[\text{weight tissue in aliquot used for water determination}]}{[\text{fat free weight of same tissue}]}$$

2. ml plasma/g tissue = [ml blood/g tissue]

$$\times [1 - (0.90^{\dagger} \times \text{hematocrit} \times 0.97^{\ddagger})]$$

3. ml blood/g tissue

$$= \frac{[\text{mg hemoglobin/100 g tissue}]}{[(\text{g hemoglobin/100 ml venous blood}) \times 1000^{\S}]}$$

Tissue blood was measured by a modification of the method of Gradwohl.[5] Benzidine dihydrocholoride in a mixture of sodium acetate and acetic acid was substituted for benzidine because of the difficulty of purifying the latter. Samples of supernatant fluid and stock hemoglobin standards were diluted immediately before use with freshly filtered 0.9% saline containing 0.1% sodium deoxycholate. A standard curve was constructed using hemoglobin concentrations of 0.02, 0.05 and 0.08 mg/ml. Hemoglobin concentrations in the supernatant samples fell on the standard curves at the following dilutions: 20X for a colorless solution, 100X to 400X for shades of pink and 800X for shades of red.

Statistical analysis of the data was performed by

TABLE 4. *Clinical Data of Three Critically Ill Patients Who Died with Acute Respiratory Failure*

Patient	Age	Sex	Diagnosis and Complications
1	63	M	Died 26 days following repair of ruptured abdominal aortic aneurysm; respiratory, renal and liver failure.
2	50	F	Died 29 days after cholecystectomy for cholelithiasis and cancer of gall bladder and breast; respiratory failure.
3	57	M	Died four days following small bowel resection for ischemic bowel due to a low flow state and three days following emergency coronary artery bypass graft; respiratory and cardiac failure.

---

* Converts g/100 to mg/g.
† Converts large vessel hematocrit to whole body hematocrit.
‡ Correction for plasma trapped in red cells.

§ Converts g to mg.

TABLE 5. *Comparison of Total and Extravascular Albumin in Pulmonary Tissue from Thoracotomy and Postmortem Lung Samples*

Group	Total Albumin mg/g fat free wet tissue	Extravascular Albumin mg/g fat free wet tissue	Water content %
Thoracotomy (n = 8) (First biopsy)	12.5 ± 1.0	9.6 ± 0.8	83 ± 1.4
Post-mortem lung (n = 30)	14.8 ± 0.6	10.3 ± 0.7	87 ± 5.1
p values	NS	NS	<0.005

p values: unpaired t test, thoracotomy vs. post-mortem lung group

computer programs which utilized Student's t test for paired and unpaired data.

This investigation was approved by the Committee on Clinical Investigation, New Procedures and Forms of Therapy of the Beth Israel Hospital.

Results

Clinical data for patients in the general and vascular group and thoracic group are shown in Table 1. The mean length of the operative procedures was not different in the two groups. As the duration of the operative procedure increased, there was a significantly greater depletion of the circulating (intravascular) albumin mass (r = 0.69, $p < 0.01$, Fig. 1). Together with the decrease in circulating albumin mass with time, there was a gradual gain of extravascular albumin in muscle tissue at the operative wound site (r = 0.63, $p < 0.01$, Fig. 2). A significant correlation was noted between the decrease in circulating albumin in the plasma and the accumulation of extravascular albumin in muscle tissue (r = 0.71, $p < 0.01$, Fig. 3). Although the circulating albumin mass decreased significantly in both groups (Table 3), the serum albumin concentration values did not change from the preoperative to the postoperative period. This was also reflected by statistically insignificant changes in the serum oncotic pressure in the same period (Table 3).

Three of the 16 patients did not receive albumin infusion intraoperatively. Although there was a significant decrease in the circulating albumin mass and serum albumin concentration in these three patients (preoperative serum albumin concentration = 3.7 ± 0.3 g/dl to 3.2 ± 0.2 g/dl postoperatively, $p < 0.025$), the decrease in serum oncotic pressure did not reach statistical significance (24.5 ± 1.2 mm Hg preoperatively to 23.4 ± 1.4 mm Hg postoperatively).

Significant increases in the content of total and extravascular albumin occurred in the skin and muscle biopsy samples from both groups of patients ($p < 0.05$ to $p < 0.001$, Table 2). Figure 4 shows that the increase of total albumin in the skin and muscle biopsy samples is almost entirely related to an increase of extravascular albumin content at the two sites (skin, r = 0.94, $p < 0.001$; muscle, r = 0.78, $p < 0.001$). However, the lung biopsies did not demonstrate any changes in the content of either total or extravascular albumin (Table 2). Although the water

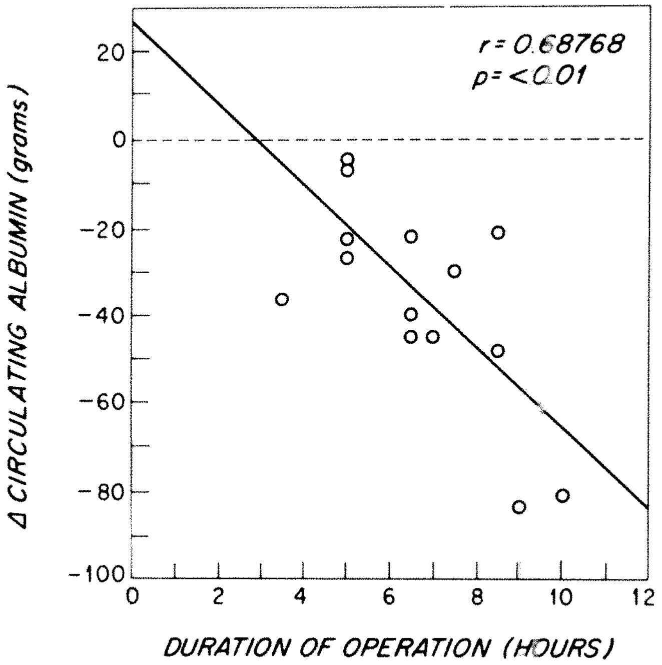


FIG. 1. Correlation of change in circulating albumin mass and duration of operative procedure.

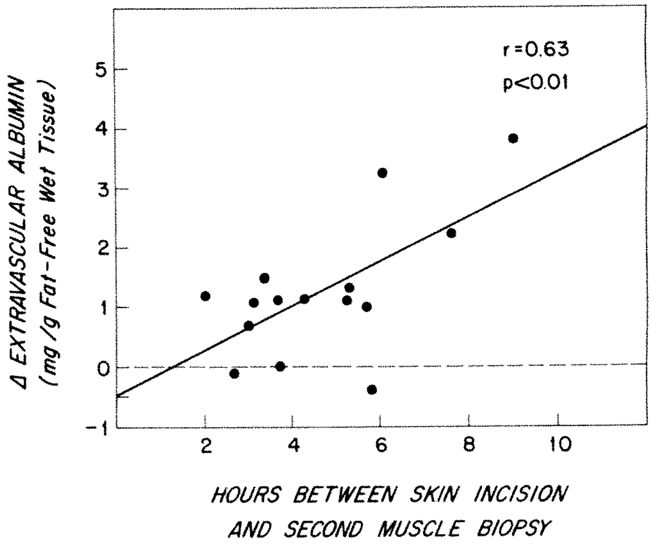


FIG. 2. Correlation between changes in extravascular albumin and its accumulation in muscle tissue with time.

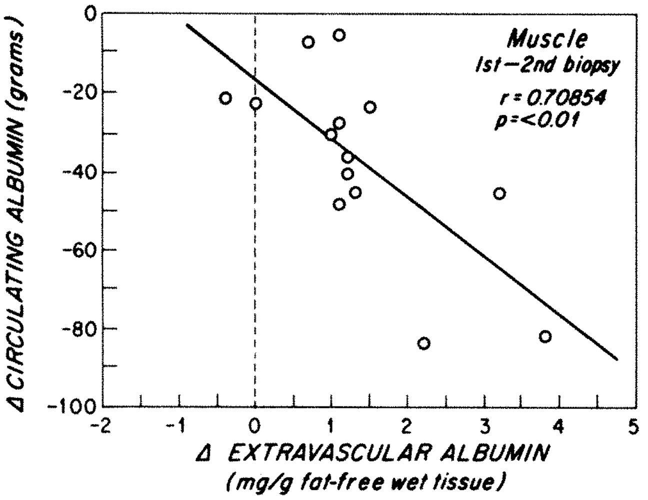


FIG. 3. Correlation between the decrease in circulating albumin in plasma and accumulation of extravascular albumin in muscle tissue.

content of the second muscle biopsies from the two groups showed a significant increase ($p < 0.05 - p < 0.025$), the skin samples did not show a significant change in water content. Water content of the second lung biopsy was significantly lower than the initial lung biopsy ($p < 0.05$).

The diagnosis and complications which resulted in the death of three postoperative patients are shown in Table 4. Even though all three of these patients were being ventilated for acute respiratory failure prior to their deaths, Table 5 indicates that there was no significant increase in the concentration of total or extravascular albumin in the postmortem samples of lung tissue in these patients in comparison to the initial biopsy samples of lung tissue from the seven patients who had lung samples taken during thoracotomy. It is of interest that patient 1, who received 50 g of salt poor albumin within the 24 hour period prior to his death, had the lowest extravascular albumin and water concentration in the pulmonary tissue of these three patients (extravascular albumin = 9.1 mg per g of fat free wet tissue; water content = 85%). Acute respiratory failure, however, was associated with the expected increase in lung water which was significantly greater ($p < 0.005$) in the three patients who died in comparison to the lung water content in the thoracotomy group. The histopathological findings were consistent with a variable but significant pattern of diffuse interstitial and intra-alveolar edema with areas of acute pneumonia in the three patients who died with acute respiratory failure.[10]

Discussion

Hypoalbuminemia frequently develops in the postoperative period in patients who undergo major operations,[8,16] especially when peritonitis is present.[14] Deficits in the circulating albumin mass in patients having major operative procedures may be prevented by the infusion of 75 to 125 g of albumin during operation.[15] It has been suggested that the increased loss of albumin from plasma in the postoperative period is related to an increased catabolism of albumin.[1] Mouridsen measured the accumulation of ^{131}I-labelled albumin in mastectomy wounds over a period of 16–26 days postoperatively and concluded that extravascular albumin was retained in the wound.[12] Since the albumin content was not specifically measured in the latter study, it is not possible to know whether the increased accumulation of radioactivity was albumin itself or large molecular degradation products of this protein.

Data from the present study show that a significant depletion of the circulating albumin mass occurs in all patients studied. The intravascular depletion of albumin is a time related phenomenon—the longer the operation, the greater the intravascular depletion. Simultaneously with the intravascular albumin depletion, there is a significant gain in the accumulation of extravascular albumin in muscle tissue (Fig. 2), a gain which is correlated significantly with the disappearance of albumin from plasma (Fig. 3). One can conclude from Figure 4 that the gain in total albumin in the skin and muscle biopsy samples from both groups of patients is almost entirely explained by the in-

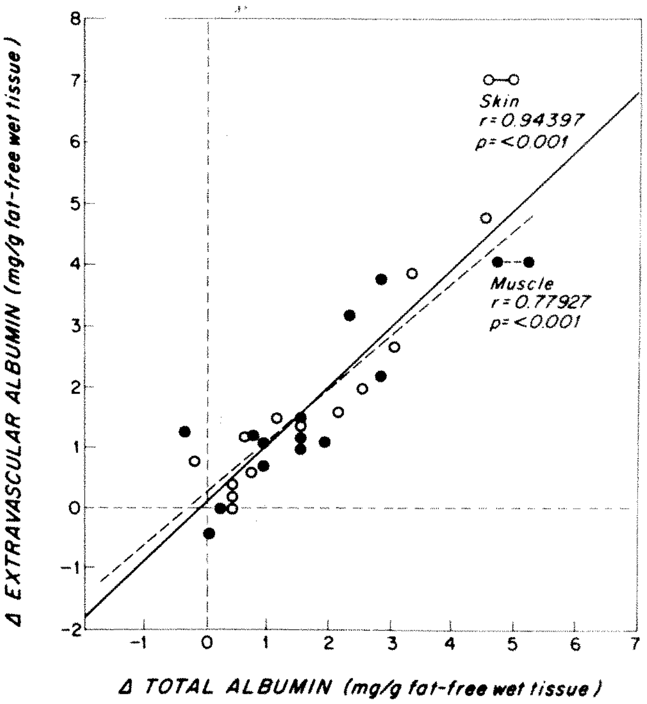


FIG. 4. Correlation between changes in total albumin and extravascular albumin in skin and muscle tissue.

crease of albumin in the extravascular space. Only in the three patients who did not receive intraoperative albumin infusions was there a significant decrease in the serum albumin concentration. These findings are consistent with the statistically insignificant changes in serum oncotic pressure observed in the entire group of patients studied. Since the amount of albumin infused intraoperatively in these patients (23 ± 10 g in group 1, and 32 ± 10 g in group 2) was modest in comparison to the amounts given in the previously reported randomized trial of patients who underwent major vascular reconstructive procedures (primarily repair of abdominal aortic aneurysms)[15] (75–125 g), it is not surprising that the two groups in the present study showed a significant decrease of the mean plasma volume postoperatively.

The changes in extravascular accumulation of albumin in skin and muscle biopsy samples from the abdominal and thoracic groups are similar. At both wound sites, the per cent increase in extravascular albumin is greater for muscle than for skin. This finding suggests the possibility that skeletal muscle permeability to albumin at wound sites may be greater than for skin. This suggestion is partly supported by the finding of significant increases in the water content in the postoperative muscle biopsies. The insignificant changes in the water content of skin, however, may reflect the difficulties encountered in the homogenization of skin samples. A small amount of residual fibrous tissue is invariably present after homogenization of the skin samples, a technical problem which does not occur with muscle. An alternative explanation for absence of an increase in the water content of skin is evaporative water loss occurring during operation. Speculation on whether the changes in the extravascular accumulation of albumin in the surgical wound could account for the entire losses of intravascular albumin are of interest. It would appear that unless these changes were to occur throughout skin and muscle tissue of the whole body, an unlikely event, the observed changes probably account for only a small fraction of the intravascular depletion. Previous work[16] suggests that the majority of the intravascular deficit is related to unreplaced plasma volume deficits.

The changes in the accumulation of extravascular albumin in the skin and muscle biopsy samples are in sharp contrast to the biopsies taken from the lung. The lung samples showed no change in the extravascular albumin content from the first to the second biopsy. The lung water content decreased significantly during this same period. These data suggest the possibility that operative trauma associated with thoracotomy does not cause edema in the lung to the same extent that it occurs in the skin and muscle, or that a different response to operative trauma occurs in pulmonary tissue. The fact that we did not find an accumulation of extravascular albumin in the lung may be explained by two possible mechanisms: 1) either albumin did not pass through the capillary membrane in excessive amounts or 2) albumin did pass through and was more actively removed by the pulmonary lymphatic circulation in comparison to lymphatic removal of albumin occurring in skin and muscle tissue.

Assuming that albumin did not pass into the extravascular pulmonary interstitial space or alveoli in excessive amounts, it may be argued that the perfusion to the resected lobe was so reduced that albumin simply did not have access to an area of increased permeability. However, there was a minimum of 60 minutes between the first biopsy and ligation of the pulmonary artery. In addition, blood flow to the pulmonary tissue to be resected would be maintained in part by bronchial artery perfusion which continues up to the time of division of the bronchus. Data from patients 12 and 15, both of whom had second lung biopsies taken from adjacent perfused lung, support the contention that under conditions of more normal perfusion, albumin did not pass into the pulmonary extravascular space in excessive amounts. (Pulmonary extravascular albumin content decreased from 8.4 to 4.7 mg/g of fat free wet tissue (patient 12) and from 8.4 to 7.0 mg/g (patient 15)).

The alternative suggestion, that albumin was more actively removed from the lung by the pulmonary lymphatic circulation cannot be definitively evaluated by our data. Although it has been shown that an intravenous infusion of 10^5-10^{10} *Pseudomonas aeruginosa* in sheep causes a significant increase in pulmonary lymph flow, separate experiments in which an increase in pulmonary microvascular pressure was produced by inflation of a left atrial balloon showed very little change in lung lymph flow.[2] Since the patients operated upon in the present study were not septic, there is no reason to believe that an increased lymphatic flow resulting in greater removal of protein from the lung should have occurred. In fact, since operative trauma might be expected to damage pulmonary lymphatics, the reverse of our findings might be anticipated. Therefore, it appears more likely that increased amounts of albumin did not gain access to the pulmonary extravascular space in the present study, even though patients in the thoracic surgical group were infused with a mean of 32 g of albumin during the operative procedure.

An additional perspective on pulmonary extravascular albumin is provided by the three postoperative patients who died in acute respiratory failure following operative procedures (Table 4). Table 5 indicates that these three patients had the same concentration of total and extravascular albumin in their pulmonary tissue in comparison to the first lung biopsy from the thoracotomy group (Table 2). These data are similar to those previously reported by Gump and coworkers.[6] Assuming a total lung weight of 400 g/M^2, for patients in the thoracotomy group and a mean body surface area of 1.8 M^2, the calculated figure for pulmonary extravascular albumin is 3.8 g per M^2, a value which is approximately 25% higher than that reported by Gump[6] for the lungs of previously healthy individuals. Similar calculations for the three patients whose lungs were examined in the postmortem period give a figure of approximately 8.8 g of pulmonary extravascular albumin per M^2. The reason for the relatively minor differences between our study and that of Gump[6] are not certain but could relate to different practices of fluid management in the two institutions in which these studies were performed. Methodological differences might also account for some difference in the two studies since Gump employed the double indicator dilution method to calculate extravascular lung water.

Except under such adverse conditions as severe systemic sepsis,[3,13] the relatively greater tightness of the pulmonary alveolar epithelial cell membrane in comparison to the pulmonary capillary endothelial cell membrane[17] and the capacity for pulmonary interstitial lymphatic removal of salt, water and protein is a significant protective feature which may prevent pulmonary intra-alveolar edema and increases in the right-to-left shunt.

Our data show that patients who die in acute respiratory failure after major operative procedures have approximately two and one half times as much extravascular albumin content in their pulmonary tissue in comparison to patients who undergo elective thoracotomy. The oncotic contribution of extravascular albumin to elevations in pulmonary water is uncertain since the precise partitioning of albumin between the pulmonary intra-alveolar space and the pulmonary interstitial space was not determined by our studies. However, the concern that an infusion of albumin might precipitously augment pulmonary interstitial albumin accumulation in patients in acute respiratory failure was not borne out by data obtained from the one patient of the three who died in which data were available to assess this issue or in the thoracotomy group who received a mean of 33 g of albumin intra-operatively.

References

1. Birke, G., Liljedahl, S-O, Plantin, L. O. and Wetterfors, J.: Albumin Catabolism in Burns and Following Surgical Procedures. Acta. Chir. Scand. 118:353, 1960.
2. Brigham, K. L., Woolverton, W. C., Blake, L. H. and Staub, N. C.: Increased Sheep Lung Vascular Permeability Caused by Pseudomonas Bacteremia. J. Clin. Invest. 54:792, 1974.
3. Clarkson, B., Thompson, D., Horwith, M. and Luckey, E. H.: Cyclical Edema and Shock Due to Increased Capillary Permeability. Am. J. Surg. 29:193, 1960.
4. Flear, C. T. and Florence, I.: A Rapid and Micro Method for the Analysis of Skeletal Muscle for Water, Sodium, Potassium, Chloride and Fat. Clin. Chim. Acta. 6:129, 1961.
5. Frankel, S., Reitman, S. and Sonnenwrith, A. C., (eds.): Gradwohl's Clinical Laboratory Methods and Diagnosis. St. Louis, C. V. Mosby Company, 1970. 7th Edition, I, pp. 465–466.
6. Gump, F. E., Mashima, Y., Ferenczy, A. and Kinney, J. M.: Pre- and Postmortem Studies of Lung Fluids and Electrolytes. J. Trauma 11:475, 1971.
7. Hansen, A. T.: A Self-recording Electronic Osmometer for Quick, Direct Measurement of Colloid Osmotic Pressure in Small Samples. Acta. Physiol. Scand. 53:197, 1961.
8. Hoedt-Rasmussen, K. and Jarnum, S.: Investigations of Postoperative Hypoalbuminemia. Acta. Chir. Scand. 122:459, 1961.
9. Katz, J., Bonnoris, G. and Sellers, A. L.: Extravascular Albumin in Human Tissues. Clin. Sci. 39:725, 1970.
10. Katzenstein, A. A., Bloor, C. M. and Leibow, A. A.: Diffuse Alveolar Damage—the Role of Oxygen, Shock and Related Factors. Am. J. Pathol. 85:195, 1976.
11. Mancini, G., Carbonara, A. O. and Heremans, J. F.: Immunochemical Quantitation of Antigens by Radial Immunodiffusion. Int. J. Immunochem. 2:235, 1965.
12. Mouridsen, H. T.: The Extravascular Retention of Serum Albumin in the Operative Wound. Acta. Chir. Scand. 134:417, 1968.
13. Riordan, J. F. and Walters, G.: Pulmonary Edema in Bacterial Shock. Lancet 1:719, 1968.
14. Skillman, J. J., Bushnell, L. S. and Hedley-Whyte, J.: Peritonitis and Respiratory Failure after Abdominal Operations. Ann. Surg. 170:122, 1969.
15. Skillman, J. J., Restall, D. S. and Salzman, E. W.: Randomized Trial of Albumin vs. Electrolyte Solutions During Abdominal Aortic Operations. Surgery 78:291, 1975.
16. Skillman, J. J. and Tannenbaum, B. J.: Unrecognized Losses of Albumin, Plasma and Red Cells During Abdominal Vascular Operations. Curr. Top. Surg. Res. 2:523, 1970.
17. Szidon, J. P., Pietra, G. G. and Fishman, A. P.: The Alveolar-capillary Membrane and Pulmonary Edema. N. Engl. J. Med. 286:1200, 1972.
18. Weichselbaum, T. E.: An Accurate and Rapid Method for the Determination of Proteins in Small Amounts of Blood Serum and Plasma. Am. J. Clin. Pathol. 16:40, 1946.

Dearterialization of the Liver for Metastatic Cancer

Clinical, Angiographic and Pathologic Observations

WILLIAM V. McDERMOTT, JR., M.D., F.A.C.S., ALLEN L. PARIS, M.D., MELVIN E. CLOUSE, M.D.,
WILLIAM A. MEISSNER, M.D.

Five cases of dearterialization of the liver for metastatic cancer are presented. Subjective and objective improvement was accomplished in three patients. Pre- and postoperative arteriography demonstrates the extent of devascularization and the routes of reestablished collateral. Microscopic studies demonstrated effects on tumor and on hepatic parenchyma and biochemical data indicate the extent and duration of hepatic dysfunction.

From the Department of Surgery, Harvard Medical School and the Harvard Surgical Service and Departments of Pathology and Radiology, New England Deaconess Hospital, Boston, Massachusetts

INTERRUPTION OF THE ARTERIAL SUPPLY to the liver has been used as a therapeutic approach to patients with portal hypertension particularly in the management of ascites, for patients with massive hemorrhage from liver trauma and in recent year for the control of inoperable primary and secondary malignant tumors of the liver.

Madding and Kennedy in 1972 carried out an extensive review of the effects of and the varying circumstances concerned with hepatic artery ligation, commented on the potential usefulness under different disease categories and outlined postoperative care indicated during the period of transient liver failure.[17] For purposes of this report, the material available in their review will not be repeated in detail but concentration will be directed primarily towards the effect of dearterialization of the liver in malignant disease. Markowitz, in 1952,[19] was the first to suggest that hepatic artery ligation might be useful in the control of metastatic cancer to the liver but Breedis and Young[6] provided the first solid basis for this approach by demonstrating that malignant tumors in the liver derive their blood supply almost exclusively from the hepatic arterial inflow. Multiple celiac arterial ligations for complications of cirrhosis were carried out by Rienhoff,[27] Berman[5] and others[2,7,8,16] but it was not until 1966, however, that both experimental and clinical reports by Nilsson[23] demonstrated the definite effects of interruption of arterial blood flow on clinical and experimental cancer. It is now clear that humans with normal hepatic parenchyma will almost invariably survive hepatic artery ligation and a significant number of patients with cancer have been treated by dearterialization. Evaluation is still extremely difficult, however, because of the tremendous variability in the natural history of malignant disease of the liver, the relatively small number of cases in all reported series and the variety of types of tumors treated in this way.

Several reports are now available on the effect of hepatic artery ligation on both primary and secondary hepatic tumors.[1,3,4,14,18] The operative mortality has been high, ranging up to 40%, and could be attributed to the extremely poor condition of some of the patients treated in this way. Most of the reports demonstrated that dearterialization does cause tumor necrosis and some authors have advised combining dearterialization with chemotherapy.[12,22,26] In our own reported experience[19] and that of three other series,[3,17,22] metastases from carcinoid tumor have almost invariably shown at least a transiently favorable response.

Plengvanit[25] and Koehler[15] demonstrated in postoperative angiographic studies that considerable return of arterial supply to the liver developed through collateral channels possibly accounting for the variable results in the limited literature available to date.

Our own experience with five cases is summarized in Table 1. As in other reports, the results are quite

---

Reprint requests: William V. McDermott, M.D., 185 Pilgrim Road, Boston, Massachusetts 02215.

Submitted for publication: January 17, 1977.

0003-4932-78-0100-0038-0105 © J.B. Lippincott Company

TABLE 1. *Summary of Effects of Dearterialization on Metastatic Cancer in Liver*

Case	Primary Tumor	Postop Angiography	Postop Microscopy	Outcome	Evaluation
M.D. 194705	Ocular melanoma.	None	None	Died six months after arterial ligations.	No improvement or palliation. In retrospect, extent of dearterialization was inadequate.
M.C. 171051	Carcinoid.	One month postop—tumor nodules show necrotic avascular center. Some arterial supply from left phrenic.	One month postop—extensive necrosis of tumor except for nodules less than 50 microns.	Living with extensive visceral and skeletal metastases 40 months after dearterialization.	Objective and subjective improvement in carcinoid syndrome for two years.
V.G. 191372	Carcinoma of endometrium.	Three weeks postop—arterial filling of liver from phrenic and pancreatic collaterals.	Multiple liver biopsies 6 months postop showed extensive necrosis and no viable tumor.	Complete relief of pain. Died of extensive cancer one year after surgery.	Excellent palliation of main symptom of right upper quadrant pain.
R.C. 209122	Cancer of tail of pancreas.	Two weeks postop—reconstitution of some arterial flow to liver via small collaterals in portahepatis and capsular arteries from a hypertrophied phrenic.	Massive necrosis of tumor extending to the periphery of the metastases. Viable tumor nodules less than 50 microns in diameter.	Died during second hospital admission, ten weeks after surgery.	No improvement despite extensive necrosis of hepatic metastases at postmortem examination.
R.L. 206359	Adenocarcinoma of left colon.	Nine months postop—hepatic arterial filling via collaterals in portahepatis and via inferior phrenic. Large vascularized adrenal metastasis.	Nine months after surgery liver biopsy showed tumor necrosis with scattered very pleomorphic cells and findings indicating decreased viability.	Died of progressive inanition 11 months after surgery.	Excellent palliation for eight months; then resumed previous course of anorexia, weight loss and progressive cachexia.

variable but there is indication that if adequate devascularization is carried out and with better selection of the cases through angiographic studies and other types of evaluation, the procedure of hepatic dearterialization may prove to be an effective adjunct to the various measures employed in the palliation of inoperable primary and metastatic cancer of the liver.

In this report, the focus will not be on analysis of clinical results since the number of cases is small and the types of malignant diseases variable, but rather on the postoperative changes in liver function tests, on the postoperative angiographic changes and, to a limited extent, on the microscopic changes observed in both the hepatic parenchyma and in the cancer.

Case Reports

Case 1. This was the first New England Deaconess Hospital admission of this 52-year-old caucasian woman who entered with a chief complaint of back pain, malaise, weight loss and abdominal enlargement. The past history was particularly pertinent in that an enucleation of the right eye for malignant melanoma had been done 25 years prior to the present admission. Significant physical findings included an absent right eye and a large nodular liver which extended below the umbilicus at the midline down to the iliac crest on the right. Liver function profile was normal except for slight elevation in alkaline phosphatase. Celiac arteriography and scintiscans were consistent with metastatic nodules in both lobes of the liver.

On 4/5/72, laparotomy was carried out and the liver was found to be diffusely and massively replaced by metastatic nodules of which biopsies were taken. Cholecystectomy and ligation of the common hepatic artery was carried out since there was no evidence of disease elsewhere in the abdomen or by x-rays elsewhere in the body.

Postoperatively, the patient did well from a clinical point of view although as anticipated, liver function test showed striking although transient derangements particularly in enzyme levels, alkaline phosphatase and bilirubin. On the fifteenth postoperative day, liver function tests except for the alkaline phosphatase had returned to normal.

On 4/30/72, the patient was discharged home to be readmitted in four to six weeks time for re-evaluation and consideration of chemotherapy. No improvement was noted following either surgery or chemotherapy and the patient gradually deteriorated at home and died in November of 1972 without postmortem examination.

Comment

This was the first case in the series and ligations only of the common hepatic and gastroduodenal arteries were carried out rather than the more extensive dearterializations of later operations. The alterations in enzymes and alkaline phosphatase were short-lived and returned to normal levels within two weeks. No appreciable clinical effects on the tumor were noted. Of general interest was the long (25 year) interval between the removal of the primary melanoma and the appearance of metastases in the liver.

Case 2. This was the fourth hospital admission of a 53-year-old caucasian woman who was admitted for re-evaluation of a carcinoid syndrome.

In retrospect, one could trace the onset of symptoms as far back as 1966 but the diagnosis was not established until 1970 when a right upper quadrant mass was palpable and a liver scan indicated metastatic disease in the liver. Quantitative urinary 5-hydroxyindolacetic acid levels were elevated and the patient was referred to the New England Deaconess Hospital. At that time, a primary carcinoid of the ileum was resected and a partial hepatic resection for removal of masses of metastatic tumor were carried out.

Following this partial hepatic resection, the patient did well for two years although symptoms of the carcinoid tumor which had almost entirely subsided, began gradually to recur.

At the time of the present admission, the 5-hydroxyindolacetic acid levels were again elevated and angiography showed multiple tumor nodules throughout both lobes of the liver. Extensive dearterialization was carried out along with cholecystectomy. Convalescence was somewhat stormy with continued fever and finally with the development of a small bowel fistula through the drain site and right upper quadrant. Reoperation was carried out, small bowel resection and anastomosis was completed and a large mass of necrotic tumor scooped out from both lobes of the liver. Multiple biopsies were done and the pathology which will be described below proved to be extremely interesting.

The patient's course has been described in a previous article.[21] Both by biochemical measurements and subjective evaluation of symptoms, there was continued improvement which continued throughout the subsequent year although carcinoid symptoms began to recur again and at the time of the present writing (1976), the patient is again incapacitated both by the carcinoid syndrome and by continued widespread skeletal and systemic metastases.

Arteriography

Samples of the arteriography carried out preoperatively and one month following operation are shown in Figures 1a and 1b. In comparison to preoperative studies, there was central avascularity suggesting necrosis throughout the previously vascular nodules but the late arterial phase showed a parenchymal blush in a hypervascular peripheral zone. The delayed arterial filling of these areas was derived largely from capsular branches fed by a hypertrophied phrenic artery.

Pathology

Biopsies from the first two operations were typical of a carcinoid with liver metastases. The various specimens from the third operation (six weeks after dearterialization) were unusually interesting as reviewed microscopically. Firstly, samples of *uninvolved hepatic parenchyma* showed more peri-portal lymphocytic infiltration than previous samples and the hepatocytes showed a number of nuclear changes consistent with nonspecific ischemic damage; in addition, there were small clumps of large, binucleated hepatocytes consistent with early regeneration. Secondly, samples from several *large metastatic tumor masses* showed only cells which were totally necrotic although still recognizable as of carcinoid origin. Thirdly, there were scattered *nodules of unaltered carcinoid*, all of which were less than 50 microns in size.

Comment

The prolonged history of this patient which is summarized so briefly in this case report indicates the palliation which can be achieved in the carcinoid syndrome, first by hepatic resection and later by

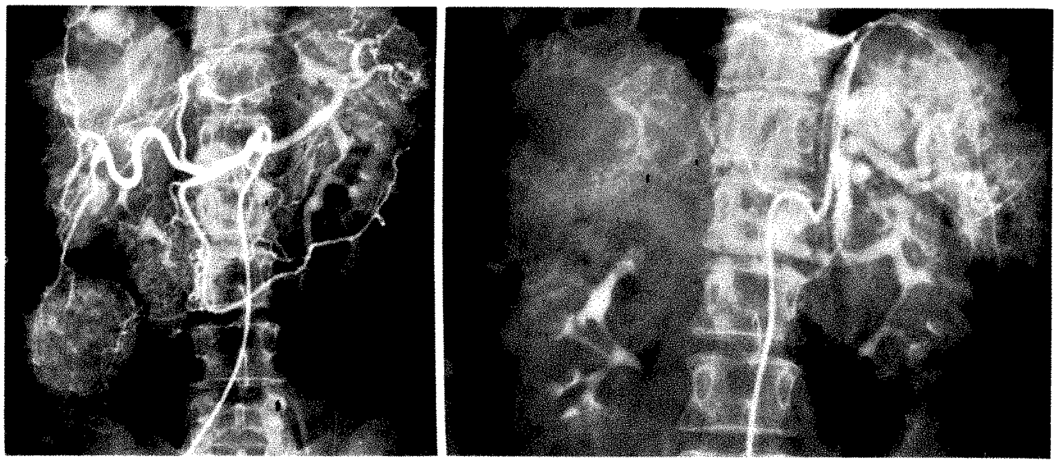
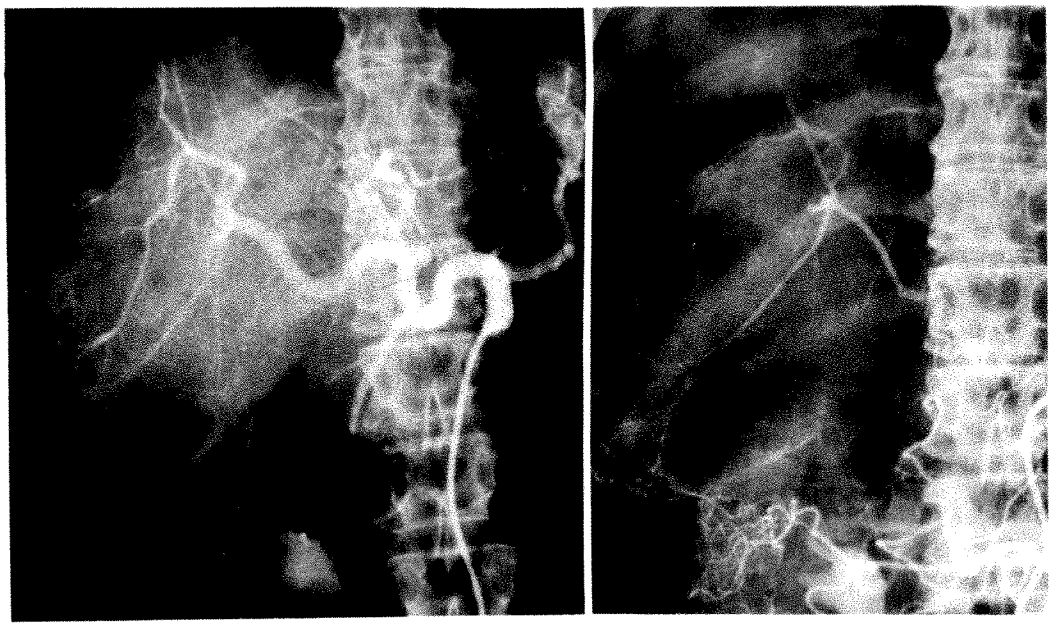


FIG. 1a and b. (a, left) Case 2. Preoperative arteriogram showing multiple hypervascular metastatic nodules throughout the liver. (b, right) Postoperative celiac arteriogram. The late arterial phase shows a parenchymal blush with hypervascular peripheral zone in the tumor nodules and a necrotic avascular center. The arterial supply is largely via capsular branches from a hypertrophied phrenic artery.



FIGS. 2a and b. (a, left) Case 3. Preoperative celiac arteriogram showing displacement and stretching of intrahepatic arterial branches, presumably by metastatic deposits of tumor. (b, right) Three weeks postoperative late arterial phase showing the hepatic arterial anatomy filled via capsular branches from hypertrophied phrenic arteries and collaterals around the head of the pancreas and porta hepatis.

hepatic dearterialization. Further reference will be made in the discussion of the difference in reaction to dearterialization of large tumor masses as compared with very small nodules.

Case 3. This 65-year-old woman was admitted because of severe constant pain in the right upper quadrant of the abdomen requiring narcotics in large doses every three hours for control.

In 1965, the patient had a hysterectomy for adenocarcinoma of the endometrium. Two years before admission, nodular metastases in the abdominal wall were treated with radiation therapy with apparent control. Three months before admission, the progressive epigastric pain which required heavy narcotic therapy began and led to the ultimate admission for evaluation and treatment.

On physical examination, there was an irregular hard nodular liver edge with a large tender mass in the right hypochondrium. On 7/18/74, laparotomy disclosed a liver which was diffusely involved with tumor, with one central mass measuring 15 × 13 cm. Liver biopsy and extensive dearterialization of the liver was carried out. Convalescence was uneventful except for a relatively prolonged ileus which has seemed to be characteristic of many of the cases of dearterialization of the liver and of a low grade fever which gradually returned to normal as did the various liver function tests. The disappearance of the severe upper abdominal pain was striking and following discharge, the patient required no further medication for pain over the subsequent months. In December of 1974, however, a different type of abdominal distress appeared, characterized more by vague, lower abdominal and flank pain which seemed unrelated to her previous symptoms. A second laparotomy was interesting in that there was a small nodule of viable tumor tissue in the scar of the previous incision but the liver itself was strikingly different than at the time of dearterialization; the large mass in the central portion had shrunk to a third of its previous size (now measuring about 5 × 4 cm) and the other areas of metastatic disease throughout both lobes were clearly diminished in total volume. Multiple liver biopsies were taken and the patient was discharged after an uneventful convalescence. The final phases of her disease were characterized by systemic metastases and she eventually died one year after the multiple arterial ligations; at no time was there any recurrence of pain and the overall palliation in this particular case was impressive.

Arteriography

Figures 2a and b show selected samples of preoperative celiac arteriography and a late arterial phase of studies carried out three weeks following operation. There are obvious residual collateral channels particularly to the proximal right hepatic artery from vessels in the porta hepatis and from small arteries around the head of the pancreas and from hypertrophied phrenic arteries.

Pathology

The hepatic parenchyma showed minor evidence of a nonspecific cellular injury. Microscopic sections of the liver taken at second operation (five months following dearterialization) showed extensive necrosis through all sections and in the tissue sent for examination, there was no viable tumor.

Comment

There would seem to be little question in this case that this patient had both complete relief of pain following dearterialization and there was objective evidence by palpation, by liver scan and by re-exploration of a remarkable regression of tumor masses in the liver. In addition, the multiple biopsies taken from residual areas of tumor showed no evidence of viable cells. Despite the objective regression of hepatic

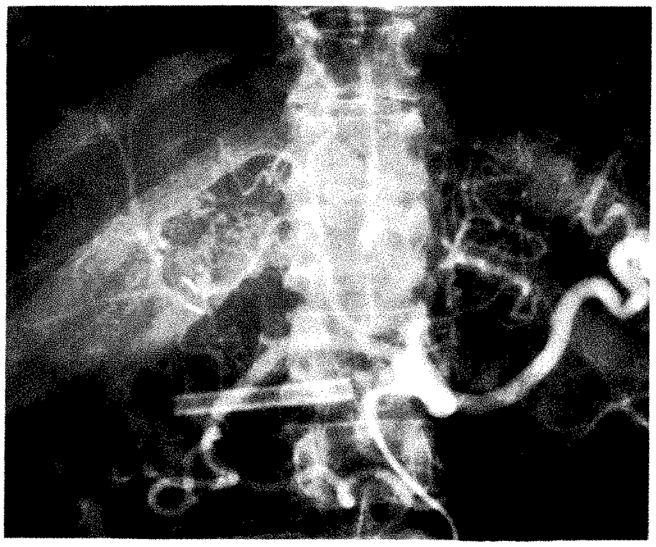


FIG. 3. Case 4. Postoperative celiac arteriogram shows ligation of the hepatic artery with reconstitution of flow via small collaterals in the porta hepatis and capsular arteries from a hypertrophied phrenic.

metastases, the patient ultimately succumbed to extensive disease one year following operation.

Case 4, R.C. This 64-year-old male was transferred from another hospital after extensive studies had revealed a mass in the right lobe of the liver which was the presumptive cause of intermittent fever of unknown origin which had begun six months prior to admission. At laparotomy, a small primary tumor was found in the tail of the pancreas and the liver was involved with extensive multiple metastatic nodules with a single large mass in the porta hepatis measuring 10 × 7 cm. Clips were placed around the primary tumor for possible radiotherapy and extensive dearterialization of the liver was carried out. Liver enzymes and function tests returned to normal within two weeks and the patient was discharged although he continued to remain febrile as during the preoperative period.

Over the subsequent weeks, he deteriorated with continued fever and malaise and was finally readmitted with extensive metastatic disease and died approximately 10 weeks after surgery. Postmortem examination was carried out and the details will be given below.

Arteriography

Postoperative celiac arteriograms shown in Figure 3 indicate ligation of the major hepatic arterial inflow but reconstitution of flow via small collaterals in the porta hepatis and sub-capsular arteries from a hypertrophied phrenic artery.

Pathology

At postmortem examination, the tumor of the liver although extensively necrotic secondary to the dearterialization still compressed the extrahepatic biliary tree in the portahepatis to the extent that it was easy to see why cholangitis had persisted and ultimately resulted in his death. Again, as in Case 2, there were viable tumor nodules measuring less than 50 microns in diameter although all larger tumor masses showed extensive and massive necrosis.

Comment

Despite the extensive necrosis of the tumor, the mass persisted as a mechanical problem in obstruction of the extrahepatic biliary tree in the porta hepatis and no palliation was achieved from the procedure.

Case 5, R.L. This 39-year-old man was first seen in the office on April 2, 1974, approximately three months after resection of a lesion of the splenic flexure at another hospital. At the time of laparotomy, at least three tumor nodules could be felt in the liver. Because of the multiplicity of the lesions and the fact that the patient was totally asymptomatic, it was elected not to institute any therapy at that time. By November of 1974 (ten months after the initial operation), there was an 8 × 5 cm mass palpable in the epigastrium obviously representing liver metastases. Because of the rapid increase in size of the tumor and because the patient was beginning to develop symptoms of epigastric distress, anorexia and weight loss, he was admitted in January of 1975, at which time laparotomy, cholecystectomy and hepatic dearterialization was carried out. Except for expected abnormalities and liver

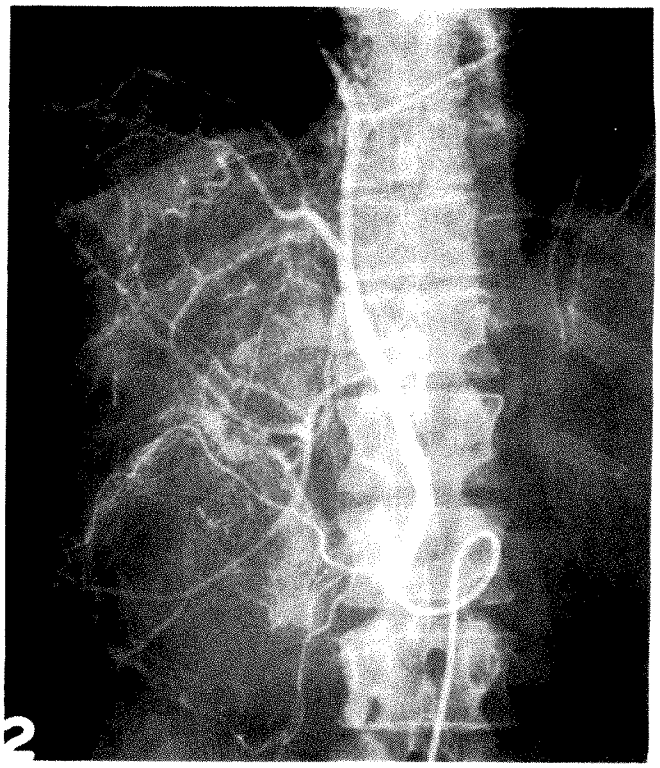


FIG. 4a. Case 5. Postoperative inferior phrenic arteriogram arising from the right renal artery. The contrast material outlines a large adrenal metastasis. There is filling of the right hepatic artery via capsular branches from the hypertrophied inferior phrenic.

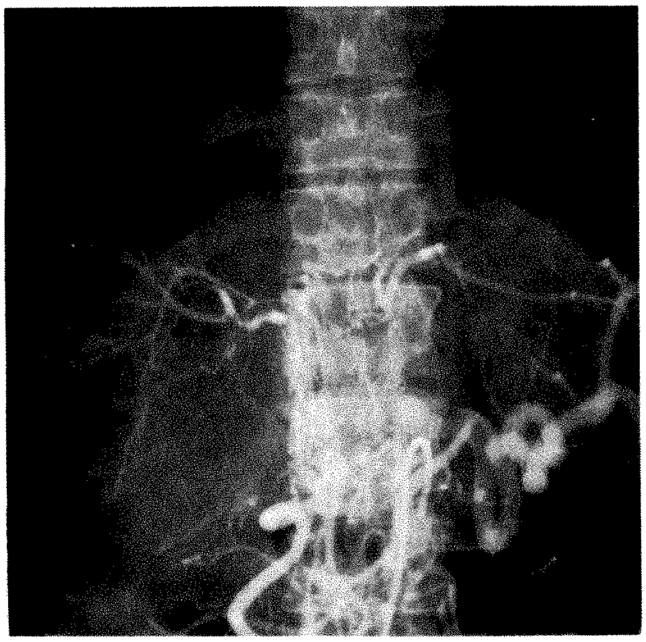


FIG. 4b. Case 5. Postoperative superior mesenteric arteriogram, a large pancreatic collateral filling the splenic artery and hypertrophied collaterals in the porta hepatis filling the right and left hepatic arteries.

function tests and enzyme responses during the first postoperative week, he did very well and was discharged in early February of 1975.

When seen in the office two months after operation, he had gained 14 lbs. in weight and there seemed to be some decrease in the size of the tumor. His preoperative symptoms had disappeared, his appetite was excellent and he seemed well in every respect. This improvement continued and he remained totally asymptomatic for approximately nine months following dearterialization at which time he again began to fail with anorexia, weight loss and increasing fatigue which limited his previously full activities. There were no further treatments carried out and the patient steadily deteriorated and died on 12/21/75.

Arteriography

Samples from postoperative arteriography shown in Figures 4a and b. In 4a, catheter was introduced into the right renal artery and a huge inferior phrenic demonstrated which outlined a large adrenal metastasis and in addition connected with the right hepatic artery via capsular branches. In Figure 4b, a superior mesenteric arteriogram, a large pancreatic collateral can be demonstrated which fills hypertrophied collaterals in the porta hepatis and ultimately results in a blush in both the right and left hepatic arterial vascular areas.

Pathology

Needle biopsies of the liver taken nine months following operation showed extensive necrosis of the metastatic cancer and a few viable cells which were striking in terms of pleomorphism and the appearance of nuclei which were large, dark and vacuolated with irregular nuclear membranes and large red nucleoli; these findings were interpreted as dramatic changes secondary to ischemia and would indicate very low viability in the remaining cells.

Comment

This man had clearcut subjective and objective palliation for nine months following dearterialization. Despite revascularization via collaterals, most of the liver cancer was necrotic; the few remaining viable cells were grossly abnormal with changes indicating border line viability.

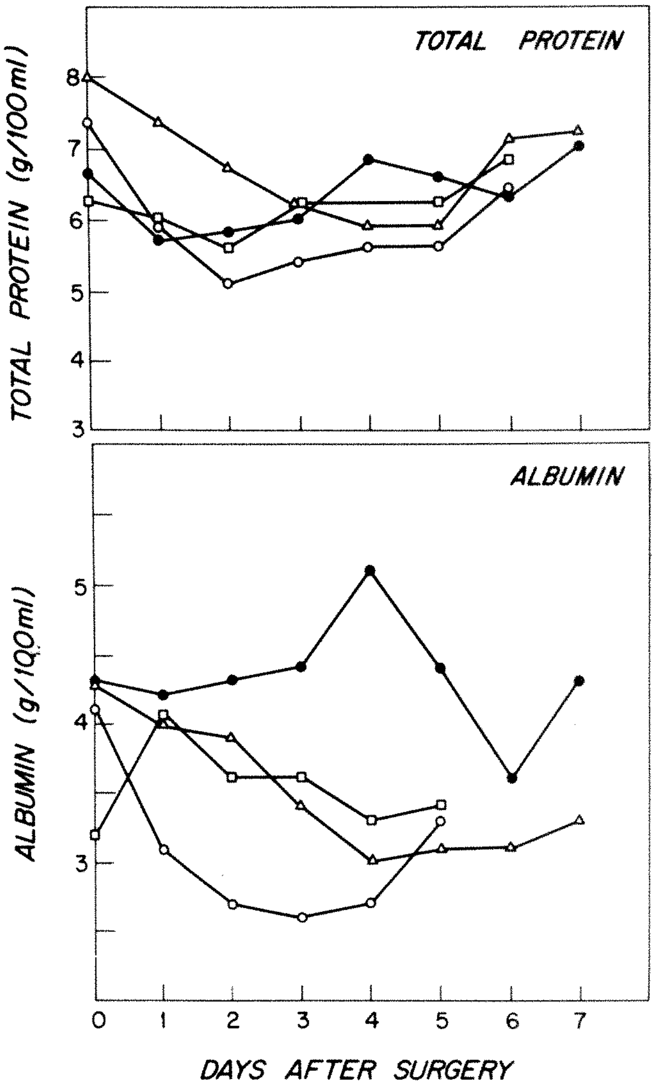


FIG. 5a. Metabolic changes after dearterialization. Alterations in plasma protein.

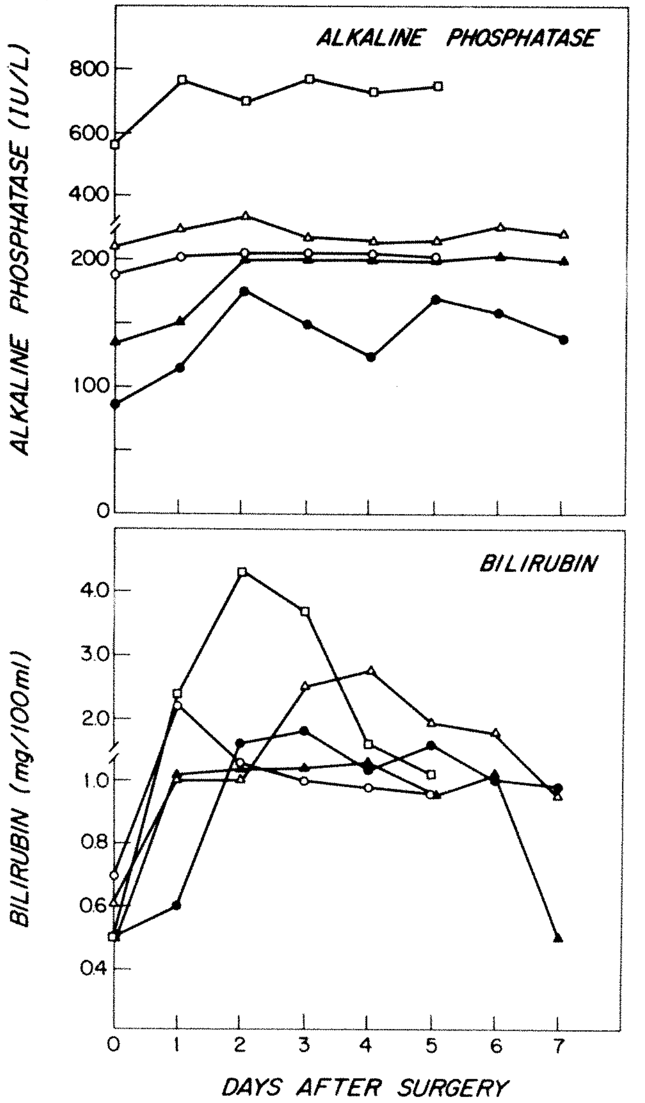


FIG. 5b. Metabolic changes after dearterialization. Changes in bilirubin, metabolism and alkaline phosphatase.

Discussion

In this small series of five cases, there was no mortality and subjective and objective improvement was evidenced in three of the patients.

Composite diagrams of the postoperative biochemical changes in enzymes and in liver function test as shown in Figures 5a–c. As can be seen, the most striking changes are in the liver enzymes which showed dramatic increases in the first few days after surgery but in general have returned to normal within a week. Protein changes show a tendency for hypoalbuminemia during the first postoperative week although this is not as striking as has been previously reported in cases of major hepatic resection.[20] The alkaline phosphatase levels were always elevated preoperatively and showed little change subsequent to the dearterialization but the bilirubin levels invariably rose and clinical jaundice was evidence throughout the first postoperative week. Within about two weeks, all these tests had returned to normal levels except for the persistent elevations in alkaline phosphatase.

Selected arteriograms have been shown which demonstrate that despite the increasingly extended efforts to achieve total arterial devascularization of the liver, some arterial flow persists and increases through various collateral channels. The most consistent of these collaterals are small branches which enlarge in the gastrohepatic ligament and begin to feed the intrahepatic arterial bed.

Initial arteriographic observations have affected our technical approach to the procedure so that we would now recommend dissection, identification and ligation of the common and proper hepatic arteries, the gastroduodenal artery, the right and left hepatic arteries, the left gastric artery and division of the triangular, falciform and hepatorenal ligaments. This degree of devascularization should provide maximum effect on the tumor and it has been well shown that the hepatic parenchyma survives even extensive dearterialization procedure as carried out in the last two cases.

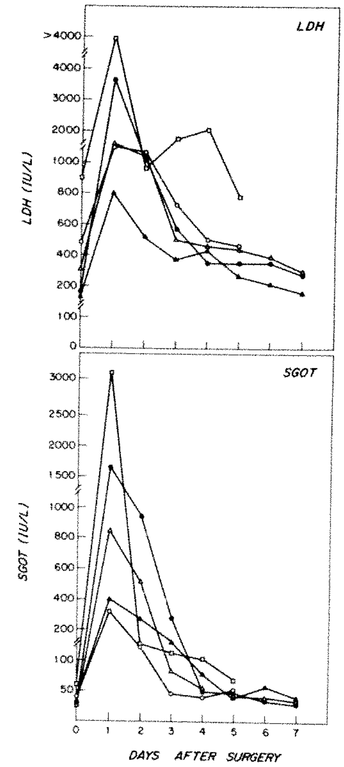


FIG. 5c. Metabolic Changes after dearterialization. Enzyme changes.

The microscopic studies were perhaps the most interesting aspect of the study and the detailed scrutiny and photomicrographs are being reported separately.[24]

In four of the five cases, liver biopsies were available at varying times postoperatively. In two cases, 2 and 4, samples were available within a few weeks of operation. In both these instances, there was extensive and almost total necrosis of large tumor masses extending out to the periphery of the tumor without evidence of viable tumor cells; in both instances, however, there were smaller nodules (less than 50 microns in diameter) which were completely viable from point of view of histological observation. This particular observation was of interest when correlated with the reports of Folkman[9-11,13] on the angiogenesis factor in tumors; in these studies Folkman demonstrated that, without developing an arterial blood supply, metastatic deposits of tumor could survive presumably by diffusion of nutrients from surrounding tissue but unless a definite arterial supply developed, these small tumor collections did not grow any larger than 2 mm in size. Our observation in these two cases in particular appeared to be confirmatory of Folkman's experimental studies in that the very small tumor nodules which were available from the biopsies showed no apparent effect from arterial ligation as compared with the large tumor masses almost all of which became totally nonviable following the procedure.

In two patients, biopsies were available six and nine months following dearterialization. In one instance (Case 3), there was extensive necrosis in all the specimens submitted and no viable tumor cells could be seen; these microscopic observations confirmed the gross observations at laparotomy in which tumor masses were shown to have shrunken remarkably from their large size at the time of dearterialization. In Case 5, needle biopsies obtained nine months after surgery again showed extensive tumor necrosis but in this instance there were scattered tumor cells which, however, were very pleomorphic with poor cellular cohesion, large irregular vacuolated nuclei, red nuclei and marked fibrosis and necrosis, all of which indicated a decreased viability secondary to continuing ischemia.

Adequate microscopic studies on hepatic parenchyma were available at varying periods from four weeks to six months and all the changes which will not be described in detail were suggestive of mild ischemic changes and in sections taken several months after dearterialization, there was evidence of regeneration with clumps of binucleated cells.

The angiographic and microscopic changes in this small series would indicate that adequate dearterialization of the liver can be accomplished with the resulting extensive tumor necrosis and maintenance of viability in the hepatic parenchyma. Three of the five cases showed objective and subjective evidence of temporary improvement suggesting that this procedure may be an added adjunctive method in the palliation of extensive metastatic disease to the liver. Adequate evaluation of clinical results would, however, necessitate extended randomized clinical trials for comparison with the natural history of the disease and with other modalities of therapy.

Summary and Conclusions

Five cases are presented with metastatic cancer of the liver for which hepatic dearterialization was carried out. Subjective and objective improvement was accomplished in three of the five cases. Postoperative angiographic studies emphasize the difficulty in achieving complete dearterialization and the rapidity with which large collateral channels will develop.

There was no evidence of serious damage to the hepatic parenchyma either by function tests or by microscopic studies attendant upon the interruption of arterial inflow. Microscopic changes in the tumor are particularly interesting inasmuch as extensive necrosis occurs in all large tumor masses but smaller nodules (less than 50 microns in diameter) maintain apparent viability. These observations have been speculatively related to the tumor angiogenesis factor.

References

1. Almersjo, O., Bengmark, S., Rudenstam, C. M., et al.: Evaluation of Hepatic Dearterialization in Primary and Secondary Cancer of the Liver. Am. J. Surg., 124:5, 1972.
2. Altemeier, W. A., McElhinney, W. T. and MacMillan, B. G.: Treatment of Portal Hypertension with Hepatic Artery Ligation. A.M.A. Arch. Surg., 71:571, 1955.
3. Aune, S. and Schistad, G.: Carcinoid Liver Metastases Treated with Hepatic Dearterialization. Am. J. Surg., 123:715, 1972.
4. Balasegaram, M.: Complete Hepatic Dearterialization for Primary Carcinoma of the Liver. Report of Twenty-four Patients. Am. J. Surg., 124:340, 1972.
5. Berman, J. K., Koenig, H. and Muller, L. P.: Ligation of Hepatic and Splenic Arteries in Treatment of Portal Hypertension. Ligation in Atrophic Cirrhosis of the Liver. Arch. Surg., 63:379, 1951.
6. Breedis, C. and Young, G.: The Blood Supply of Neoplasms in the Liver. Am. J. Pathol., 30:969, 1954.
7. Chenoweth, A. I.: Early Results Following Therapeutic Ligation of the Hepatic Artery. Ann. Surg., 135:756, 1952.
8. Desforges, G., Campbell, A. J. A. and Robbins, S. L.: Hepatic Artery Ligation for Portal Hypertension. Ann. Surg., 137: 507, 1953.
9. Folkman, J.: Anti-angiogenesis: New Concept for Therapy of Solid Tumors. Ann. Surg., 175:409, 1972.
10. Folkman, J.: Tumor Angiogenesis Factor. Cancer Res., 34: 2109, 1974.

11. Folkman, J., Merler, E., Abernathy, C. and Williams, G.: Isolation of a Tumor Factor Responsible for Angiogenesis. J. Exp. Med., 133:275, 1971.
12. Fortner, J. G., Mulcare, R. J., Solis, A., et al. Treatment of Primary and Secondary Liver Cancer by Hepatic Artery ligation and infusion chemotherapy. Ann. Surg., 178:162, 1973.
13. Gimbrone, M. A., Jr., Leapman, S. B., Cotran, R. S. and Folkman, J.: Tumor Dormancy In Vivo by Prevention of Neovascularization. J. Exp. Med., 136:261, 1972.
14. Huguier, M. and H. Hirsch-Marie.: Hepatome sur Cirrhose. Taux des Alpha-foeto-proteines Seriques apres Desarterialisation Hepatique. La Novelle Presse medicale. 1:2905, 1972.
15. Koehler, R. E., Korobkin, M. and Lewis, F.: Arteriographic Demonstration of Collateral Arterial Supply to the Liver After Hepatic Artery Ligation. Radiology, 117:49, 1975.
16. Madden, J. L.: Ligation of the Hepatic and Splenic Arteries in the Treatment of Cirrhosis of the Liver. Surg., Gynecol Obstet., 96:594, 1953.
17. Madding, G. F. and Kennedy, P. A.: Hepatic Artery Ligation. Surg. Clin. North Am., 52:719, 1972.
18. Madding, G. F., Kennedy, P. A. and Sogemeier, E.: Hepatic Artery Ligation for Metastatic Tumor in the Liver. Am. J. Surg., 120:95, 1970.
19. Markowitz, J.: The Hepatic Artery. Surg., Gynecol Obstet., 95:644, 1952.
20. McDermott, W. V., Jr., Greenberger, N. J., Isselbacher, K. J. and Weber, A. L.: Major Hepatic Resection: Diagnostic Techniques and Metabolic Problems. Surgery, 54:56, 1963.
21. McDermott, W. V., Jr. and Hensle, T. W.: Metastatic Carcinoid to the Liver Treated by Hepatic Dearterialization. Ann. Surg., 180:305, 1974.
22. Murray-Lyon, I. M., Dawson, J. L., Parsons, V. A., et al.: Treatment of Secondary Hepatic Tumours by Ligation of Hepatic Artery and Infusion of Cytotoxic Drugs. Lancet 2:172, 1970.
23. Nilsson, L. A. V.: Therapeutic Effect of Hepatic Artery Ligation in Patients with Secondary Liver Tumors. Rev. Surg., 23:374, 1966.
24. Paris, A. L., Meissner, W. A. and McDermott, W. V., Jr.: Histologic Changes Seen in the Hepatic Parenchyma and in Metastatic Nodules Following Hepatic Dearterialization. Am. J. Surg. Pathol. (In Press)
25. Plengvanit, U., Chearanai, O., Sindhvananda, K., et al.: Collateral Arterial Blood Supply of the Liver after Hepatic Artery Ligation: Angiographic Study of Twenty Patients. Ann. Surg., 175:105, 1972.
26. Ramming, K. P., Sparks, F. C., Eilber, R. R. et al. Hepatic Artery Ligation and 5-Fluorouracil Infusion for Metastatic Colon Carcinoma and Primary Hepatoma. Am. J. Surg., 132:236, 1976.
27. Rienhoff, W. F., Jr. and Woods, A. C., Jr.: Ligation of Hepatic and Splenic Arteries in Treatment of Cirrhosis with Ascites. JAMA 152:687, 1953.

A "New" Diaphragm Following Prosthetic Repair of Experimental Hemidiaphragmatic Defects in the Pup

ROBERT J. TOULOUKIAN, M.D.

From the Department of Surgery, Section of Pediatric Surgery, Yale University School of Medicine and the Yale-New Haven Hospital, New Haven, Connecticut

Hemidiaphragmatic defects were created in ten pups and repaired with Silastic Sheeting (Dow–Corning .007u) to determine the long-term results of prosthetic replacement of the diaphragm in growing subjects. All animals survived the operation without complication and grew and developed normally, weighing between 35 and 40 pounds at one year of age. The prosthesis gradually became located in the extreme left anterolateral costophrenic sulcus in nine of the ten dogs studied by sequential chest x-rays. Slight paradoxical movement was visible by fluoroscopy without eventration of the diaphragm. One animal developed an asymptomatic posterolateral diaphragmatic hernia nine months following operation. The other animals were sacrificed at one year of age. The liver, spleen and stomach were partially covered by a "new" muscle containing diaphragm having a mean area of 176 ± 8.3 cm, compared to the original defect which measured 15.89 ± 1.2 cm. Skeletal muscle cells extended into the margins of the prosthesis. The dorsolateral location of the "new" diaphragm is evidence that postnatal skeletal muscle growth may be derived from persisting precursor tissues.

OCCASIONALLY, THE DIAPHRAGMATIC defect in a newborn with a congenital diaphragmatic hernia is too large for primary closure to be achieved. The actual incidence of an extremely large foramen of Bochdalek defect or congenital agenesis of the entire hemidiaphragm based on review of several large series is extremely low.[2,4,6,10,11,18] A family incidence of agenesis of the hemidiaphragm has been reported[8] suggesting that this disorder is inherited as an autosomal recessive trait.

The size of the anatomic defect in an infant with the typical clinical and radiographic features of a posterolateral diaphragmatic hernia is never known prior to operation. A fluid and air-tight barrier which has the strength to prevent recurrence yet is flexible enough to move with respiration must be provided if the baby with a hemidiaphragmatic defect is to survive. We believe that a prosthesis is preferable to a variety of tissue reconstructive techniques involving the chest wall or adjacent viscera.

The following study using Silastic Sheeting for prosthetic repair of experimental hemidiaphragmatic defects in the pup was undertaken to determine: 1) the long-term clinical result of prosthetic substitutes of the diaphragm in the growing experimental animal, 2) the possibility that persisting marginal skeletal muscle may grow and reconstitute a portion of the diaphragmatic defect and 3) whether or not nonporous prostheses such as Silastic Sheeting are suitable for diaphragmatic replacement.

Materials and Methods

Ten pups weighing four to six pounds at six to eight weeks of age underwent excision and replacement of the entire left hemidiaphragm with Silastic Sheeting (Dow–Corning .007 u) through a midline abdominal incision under endotracheal halothane anesthesia. The prosthesis, an inert silicone rubber material, was anchored laterally to the ribs with encircling 4–0 Tevdek sutures and medially to the septum transversum and made identifiable for serial x-rays by affixing silver clips to its margins (Fig. 1).

Submitted for publication: March 3, 1977.

0003-4932-78-0100-0047-0075 © J.B. Lippincott Company

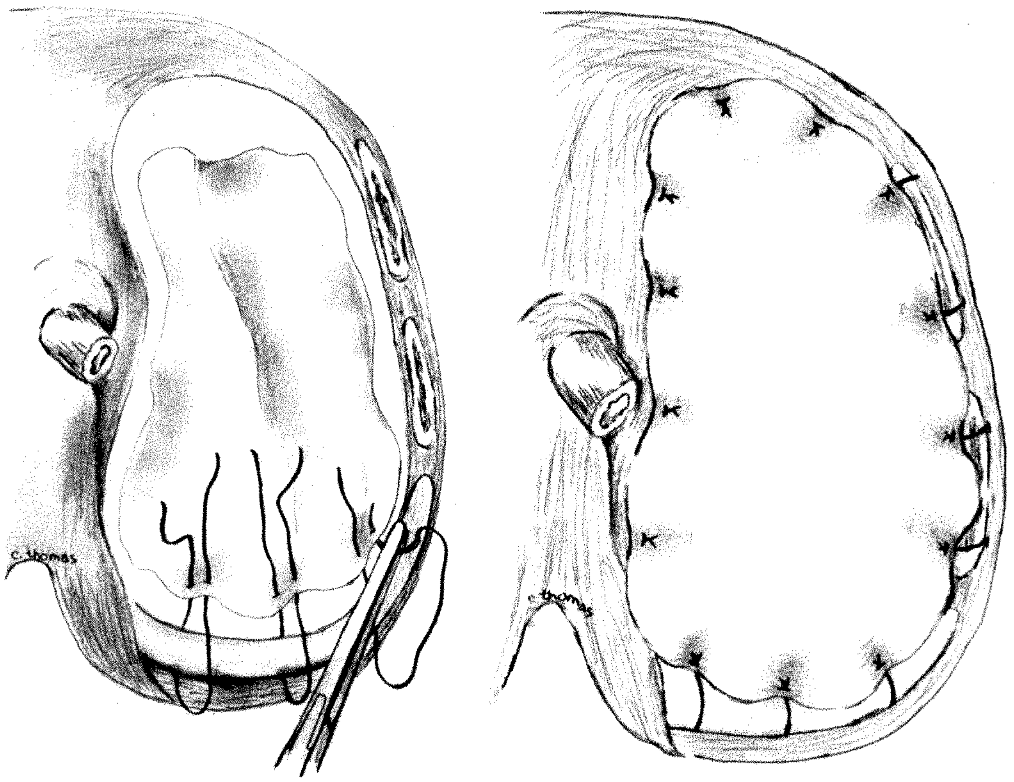
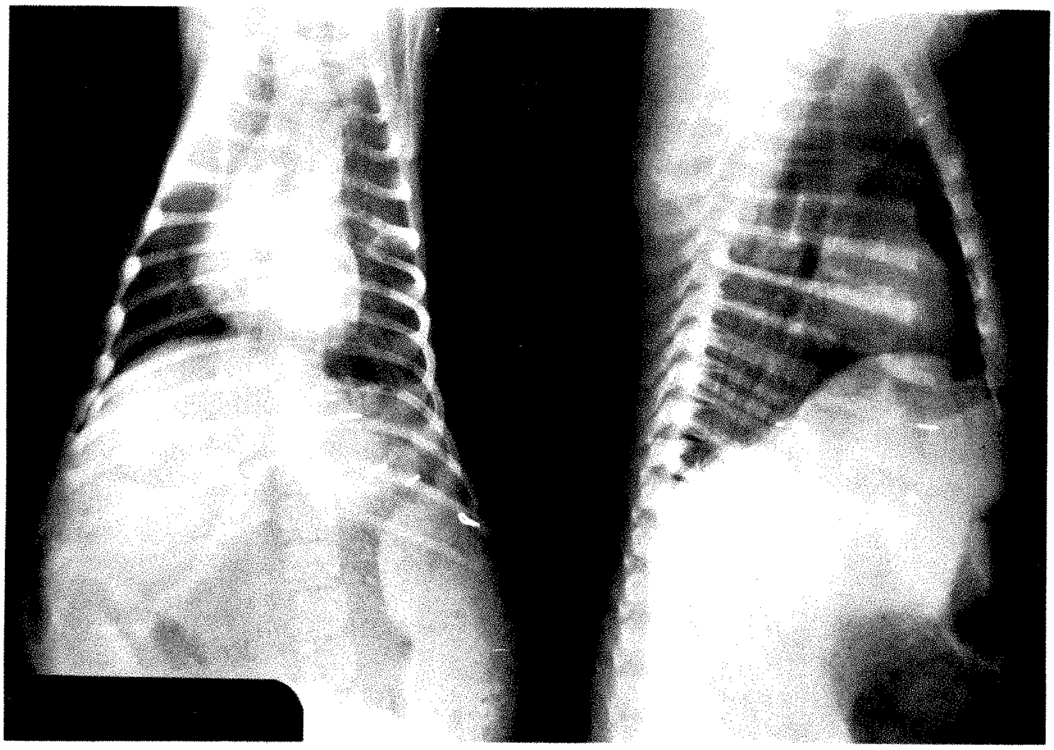


FIG. 1a and b. Technique of prosthetic repair of a left-sided hemidiaphragmatic defect through a transabdominal incision. Material is first anchored to the ribs (a, left) with encircling Tevdek sutures and the repair completed with interrupted sutures to the medial margin of the diaphragm and crus (b, right).

Results

All animals survived the operation without complication and grew and developed normally, weighing between 35 and 40 pounds at one year of age. Their activity level was identical to the control animals. The prosthesis gradually became located in the extreme left anterolateral costophrenic sulcus in nine of the ten dogs



FIGS. 2a–c. P–A and lateral view of the chest of a four week old pup immediately following hemidiaphragmatic replacement with Silastic sheeting (a) and ten months later (b and c). Note that the silver clips at the margin of the prosthesis are gradually displaced into the left costopphrenic sulcus.

studied by sequential chest x-rays (Fig. 2). Slight paradoxical movement was visible by fluoroscopy performed at six, nine and 12 months under light intravenous pentothal anesthesia, but eventration of the diaphragm did not occur. One animal developed an asymptomatic posterolateral diaphragmatic hernia between the prosthetic and the marginal tissues six months after operation and was sacrificed. The other animals were sacrificed at one year of age. The liver, spleen and stomach were adherent to the undersurface of a membrane comprised of normal appearing diaphragmatic muscle and fibrous adhesions. The "new" diaphragm was intimately incorporated into the margins of the prosthesis, and could not be separated with opposing manual traction. The mean area of the Silastic patch used in the nine animals studied was 15.89 ± 1.2 cm compared to 176 ± 8.3 cm for the entire area of the "new" diaphragm at one year of age. The grossly normal appearing diaphragmatic muscle accounted for approximately 50% of the entire hemidiaphragmatic space.

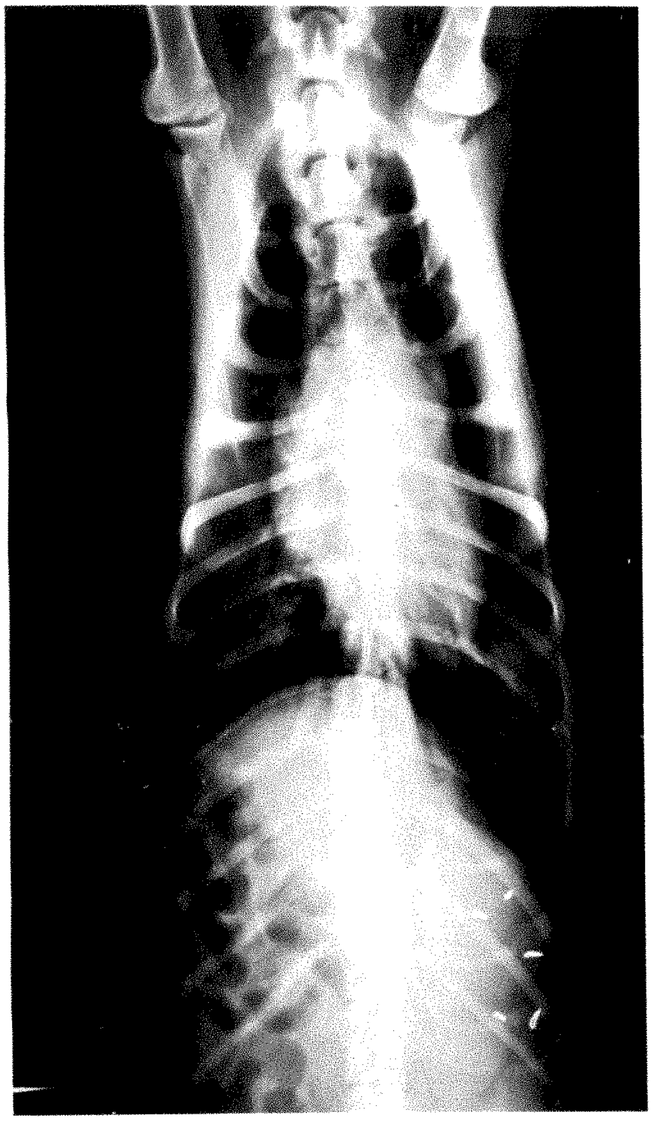


FIG. 2b. See legend for Figures 2a–c.

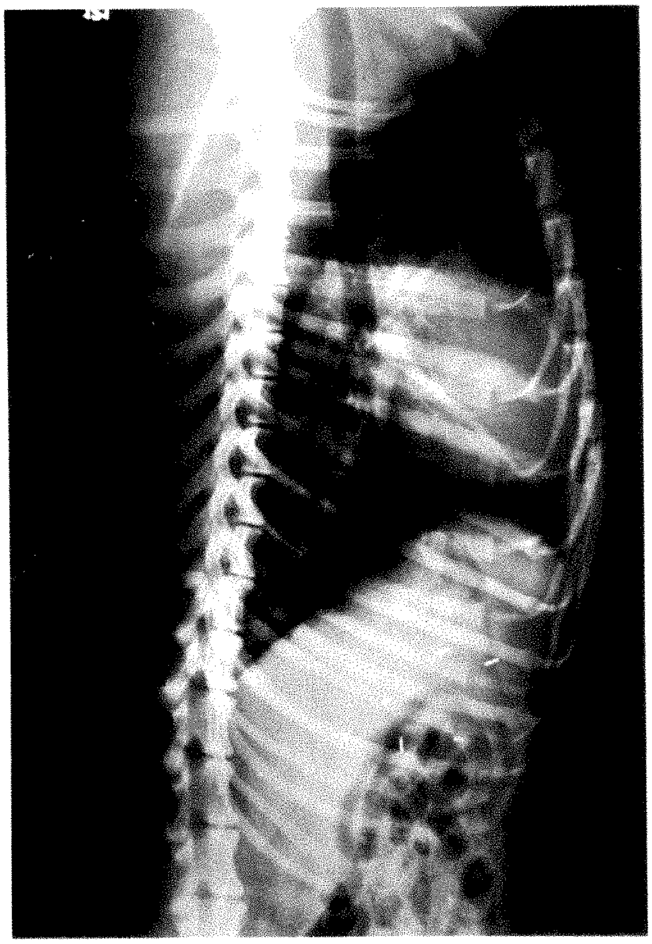


FIG. 2c. See legend for Figures 2a–c.

Light microscopy using both routine Hematoxylin and Eosin as well as Mallory trichrome stains revealed bundles of normal skeletal muscle in the "new" diaphragm and immature cells containing large amounts of cytoplasm within the margins of the Silastic patch. These cells stained pinkish-red and had the histologic appearance of immature rhabdomyocytes (Fig. 3).

Discussion

Primary repair of a congenital diaphragmatic defect can be accomplished without difficulty in over 90% of cases. Occasionally, the posterolateral margin of remaining diaphragm is curled on itself and must be dissected free to gain adequate length. Defects too large to close primarily have been repaired by a number of different reconstructive procedures often with a high risk of recurrence, morbidity and mortality. Some of these are of historical importance. Neville and Clowes[15] used the left lobe of the liver to repair

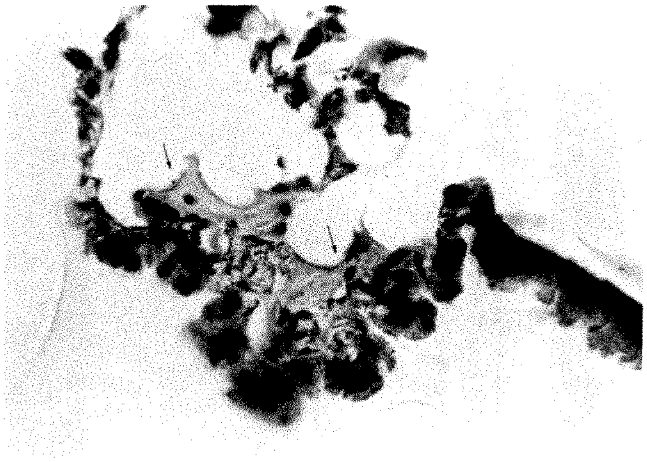


FIG. 3. Immature skeletal muscle cells (arrows) with abundant cytoplasm which stain pinkish-red with Mallory trichrome solution are found within the margins of the Silastic sheeting.

a hemidiaphragmatic defect in a newborn but reported a "subsequent rather high position of the newly created diaphragm." Four of 16 adult mongrel dogs with experimentally created hemidiaphragmatic defects had prompt recurrence of the hernia using this technique. Other authors recommended occluding the opening with renal fascia,[19] free cutis grafts[9] and "stomach, spleen, colon and omentum."[12] Gradual eventration if not prompt recurrence is certain to occur if the tissue partition does not have adequate tensile strength.

More extensive procedures using fascia and muscle have also been attempted. Rosenkrantz and Cotton[16] created abdominal muscle pedicle flaps while Holcomb[13] turned flaps of tissue "consisting of ribs, cartilages, intercostal muscles, nerves and blood vessels which could be fashioned from the lower anterior and lateral rib cage—and hinged anteriorly might serve as a diaphragm." Meeker and Snyder[14] slid the anterior subcostal layer of muscle and fascia posteriorly much in the same way as the "doors of some garages are unfolded." Operations such as these are technically difficult and lose more time and blood in a sick newborn than is safe if an equally good alternative were available.

The ideal prosthetic material for replacement of a large hemidiaphragmatic defect in a growing baby must be tough, durable, inert and pliable. Mesh substances such as Marlex (polypropylene) or Mersilene (dacron) have been used as fascial substitutes in the repair of large ventral and inguinal hernias and with apparent success in the repair of large hemidiaphragmatic defects in the neonate.[4,6,11,13,17] Nylon tulle, a widely porous, pliable synthetic net and a closely woven calendered nylon fabric were tested as diaphragmatic substitutes in adult dogs.[1] Each functioned satisfactorily but evidence of new muscle growth was not reported. These mesh prostheses were eventually incorporated into the regional tissues by the host fibroblasts during the organization phase of wound healing but controlled studies of their fate as a diaphragmatic substitute in growing experimental subjects has never been conducted.

Silastic sheeting is a nonreinforced medical grade silicone rubber material which is nonporous and because of its inertness,[5] could be displaced by active growth forces. This property of Silastic was demonstrated by the movement of the prosthesis into the anterolateral chest in growing dogs. The presence of skeletal muscle in the posterolateral chest is taken as evidence that the "new" diaphragm may be derived from persisting precursor tissues which have an anteriorly directed vector force. This hypothesis is supported by the embryologic evidence that the muscle fibers of the diaphragm are derived from the cervical myotomes which grow between the preformed pleuroperitoneal folds and by subsequent ingrowth of muscle from undifferentiated mesenchyme in surrounding tissues.[20] The skeletal muscle in the "new" diaphragm of the pups is probably derived from persisting secondary muscle ingrowth arising in the chest wall. Finding cells which stain pinkish-red with Mallory trichrome solution extending into the Silastic sheeting was not anticipated since previous experience using this material sutured to fascia[7] indicates that biologic union does not occur. Final evidence that these cells are definitely of skeletal muscle origin and not fibroblasts requires the finding of myofibrils on ultramicroscopy.

Prosthetic repair of experimental hemidiaphragmatic defects with nonporous silon sheets was achieved without recurrence of the hernia in nine of ten pups studied. These findings provide an option to mesh materials as diaphragmatic substitutes, particularly when prompt restoration of intrathoracic negative pressure must be achieved. The technique of anchoring the patch to the ribs and medially to the crura, as described, is recommended whether or not silon or mesh materials are used in the repair.

References

1. Adler, R. H. and Firme, C. N.: The Use of Nylon Prostheses for Diaphragmatic Defects. Surg. Gynecol. Obstet. 104: 669, 1957.
2. Allen, M. S. and Thomson, S. A.: Congenital Diaphrag-

matic Hernia in Children Under One Year of Age: a 24 Year Review. J. Pediatr. Surg. 1:157, 1966.

3. Benjamin, H. B.: Agenesis of the Left Hemidiaphragm. J. Thorac. Cardiovasc. Surg. 46:265, 1963.
4. Boles, E. T., Jr., Schuller, M. and Weinberger, M.: Improved Management of Neonates with Congenital Diaphragmatic Hernias. Arch. Surg. 103:344, 1971.
5. Brown, J. B., Ohlwiler, D. A. and Fryer, M. P.: Investigation of and Use of Dimethyl Siloxanes, Halogenated Carbons and Polyvinyl Alcohol as Subcutaneous Prostheses. Ann. Surg. 152:534, 1960.
6. Cerille, G. J.: Foramen of Bochdalek Hernia: A Review of the Experience at Childrens Hospital of Denver, Colorado. Ann. Surg. 159:385, 1964.
7. Cordero, L., Touloukian, R. J. and Pickett, L. K.: Staged Repair of Gastroschisis with Silastic Sheeting. Surgery 65:676, 1969.
8. Feingold, M.: Aplasia of the Diaphragm. Pediatrics 47:601, 1971.
9. Geever, E. D. and Merendino, K. A.: The Repair of Diaphragmatic defects with Cutis Grafts. Surg., Gynecol. Obstet. 95:308, 1952.
10. Graivier, L., Dorman, G. W. and Votteler, T. P.: Congenital Diaphragmatic Hernia in Children. Surg., Gynecol. Obstet. 132: 408, 1971.
11. Harberg, F. J., Meagher, D., Wetchler, S., et al.: Congenital Anomalies of the Diaphragm. Personal Experience with Thirty-five Consecutive Cases. Am. J. Surg. 132:747, 1976.
12. Hedblom, C. A.: Diaphragmatic Hernia. JAMA 85:947, 1925.
13. Holcomb, G. W., Jr.: A New Technique for Repair of Congenital Diaphragmatic Hernia with Absence of the Left Hemidiaphragm. Surgery 51:534, 1962.
14. Meeker, I. A., Jr. and Snyder, W. H. Jr.: Management of Diaphragmatic Defects in Infants. Am. J. Surg. 104:196, 1962.
15. Neville, W. E. and Clowes, G. H. A. Jr.: Congenital Absence of Hemidiaphragm and Use of a Lobe of Liver in its Surgical Correction. Arch. Surg. 69:282, 1954.
16. Rosenkrantz, J. G. and Cotton, E. K.: Replacement of Left Hemidiaphragm by a Pedicled Abdominal Muscular Flap. J. Thorac. Cardiovasc. Surg. 48:912, 1964.
17. Shaffer, J. O.: Prosthesis for Agenesis of the Diaphragm. JAMA 188:1000, 1964.
18. Snyder, W. J. Jr. and Greaney, E. R. Jr.: Congenital Diaphragmatic Hernia: 77 Consecutive Cases. Surgery 57: 576, 1964.
19. Weinberg, J.: Diaphragmatic Hernia in Infants: Surgical Treatment with the Use of Renal Fascia. Surgery 3:78, 1938.
20. Wells, L. J.: Development of the Human Diaphragm and Pleural Sacs. (Carnegie) Contributions. Embryology 35:107, 1954.

The Role of Splenectomy in the Treatment of Thrombocytopenic Purpura Due to Systemic Lupus Erythematosus

WILLIAM P. HOMAN, M.D., PETER DINEEN, M.D.

Splenectomy in the treatment of thrombocytopenic purpura associated with lupus erythematosus has afforded satisfactory overall results in a group of ten patients. Postoperative deaths occurred in two patients, each of whom had significant underlying problems. Clinical manifestations of SLE-induced thrombocytopenic purpura included ecchymoses, petechiae, menorrhagia, epistaxis, and hematuria. Splenectomy in this disorder should be reserved for cases in whom corticosteroids do not produce satisfactory results, or in whom unacceptably high doses are required. Follow-up indicates long term control of thrombocytopenic purpura following splenectomy.

From the Department of Surgery, The New York Hospital–Cornell Medical Center, New York, New York

SPLENECTOMY IS AN ACCEPTED therapeutic approach for certain refractory hematologic disorders. Spencer Wells successfully removed a spleen for hereditary spherocytosis in 1887, and Kaznelson in 1916, while a medical student, prevailed upon his professor to perform the first splenectomy for thrombocytopenic purpura. Growing knowledge of the function of Galen's "organ full of mystery" has allowed application of splenectomy to other hematologic disorders both primary and secondary to other illnesses.

Little information is available to the surgeon who is asked to evaluate for possible splenectomy a patient with thrombocytopenic purpura due to systemic lupus erythematosus (SLE). Recent medical textbooks mention the subject of splenectomy for thrombocytopenic purpura in SLE only in passing,[7,12] and surgical textbooks not at all.[10,13] The subject was covered in some depth by Best and Darling in 1962,[2] but only occasional reports have appeared since then.[1,6] Even reports of large series of splenectomies for hematologic disorders only briefly mention SLE-associated thrombocytopenia.[5,11] This report was stimulated by our inability to assembly a significant amount of recent information on this subject, and by the growing number of patients with SLE that we are called upon to see.[7]

Patients

The charts of all patients discharged from The New York Hospital–Cornell Medical Center (NYH–CMC) with a diagnosis of SLE from 1932 through 1975 were reviewed. In all there were 916 patients. Of these patients, ten (1.1%) underwent splenectomy for thrombocytopenic purpura that was not satisfactorily controlled by medical therapy. These ten patients form the basis of this report. In each a diagnosis of SLE was confirmed using accepted clinical criteria and laboratory tests.[12] There were no cases of drug-induced lupus among our ten patients, and no patient had another identifiable cause for thrombocytopenia. There were three men and seven women, all Caucasian. Ages at the time of splenectomy ranged from 16 to 66 years with a mean of 30 years. In each patient the onset of thrombocytopenic purpura came during the course of established SLE.

Signs and Symptoms

Bleeding manifestations were dominant in the patients undergoing splenectomy for SLE-induced thrombocytopenia and are summarized in Table 1. All had skin evidence of a hemostatic defect–petechiae, purpura, or ecchymoses. In addition, menorrhagia, bleeding gums, hematuria and epistaxis were common. Additional clinical manifestations reflected the systemic nature of SLE, and are summarized in Table 2.

Reprint requests: Peter Dineen, M.D., Department of Surgery, Cornell University Medical College, 1300 York Avenue, New York, New York 10021.

Submitted for publication: February 14, 1977.

0003-4932-78-0100-0052-0075 © J.B. Lippincott Company

TABLE 1. *Clinical Summary of Patients Seen at NYH–CMC*

					Platelet Count (× $10^3/mm^3$)			
No/Year	Age at Diagnosis/ Sex	Age at Splenectomy	Bleeding Manifestations	Steroid (Amount, Duration)	Presenting	After Steroid	Postop	Follow-up (Platelets)
1. 1946	42/M	42	Purpura, petechiae, hematochezia, hematuria, epistaxis, gum bleeding	Steroids not given	48	Steroids not given	148	30 year (497,000)
2. 1953	40/F	40	Purpura, petechiae, guaiac + stool, menorrhagia	Cortisone (300 mg daily × 6 wks)	5	10	345	Died 1 yr postop of CVA (785,000)
3. 1955	23/F	23	Purpura, petechiae, melena, menorrhagia, gum bleeding, epistaxis	Cortisone (200 mg daily × 1 mo)	19	315	1605	16 yr (390,000)
4. 1963	16/M	16	Purpura, petechiae, hematuria, epistaxis	Prednisone (40–80 mg daily × 1 yr)	0	222	678	9 yr adequate smear
5. 1967	62/F	66	Purpura, petechiae, hematochezia	Prednisone (80 mg daily × 1 yr)	12	158	392	No followup
6. 1971	22/F	25	Purpura, petechiae, hematuria, menorrhagia	Prednisone (40–80 mg daily × 4 yrs)	33.8	616	375	1 yr; no steroids
7. 1972	18/M	18	Purpura, hematuria	Prednisone (80 mg daily × 28 days; 160 mg daily × 8 days)	1	1	197	Died postop peritonitis
8. 1972	21/F	21	Purpura, petechiae, guaiac + stool, hematuria, epistaxis, gum bleeding	Prednisone (100 mg daily × 6 wks)	3	48	48	Died postop pneumonia
9. 1974	15/F	21	Purpura, menorrhagia, bleeding after dental extraction	Prednisone (30–60 mg daily × 7 mos)	9	264	900	2 yr (250,000)
10. 1974	32/F	32	Purpura, menorrhagia	Prednisone (50 mg daily × 5 mos)	Unknown	192	498	1 yr (300,000)

Laboratory

Initial platelet counts are given in Table 1. These ranged from 0 to 48,000/mm³ (normal 200,000–400,000). Bone marrow aspirations were performed in all but one patient. In five patients megakaryocyte numbers were increased in the bone marrow aspirate, in three they were normal, and in one the results are unknown as the aspiration was performed at another hospital prior to the patient's transfer to NYH–CMC. The hemoglobin level was below 12g% in four patients, between 12 and 14g% in four, and greater than 14g% in two. The white blood cell and differential counts were normal in all patients, although steroid therapy induced a mild leukocytosis preoperatively.

All patients had a positive LE cell test at some point during the course of their disease, except one patient in whom the test was performed after the institution of high dose corticosteroids. In this patient a positive test for antinuclear antibodies, and a false positive VDRL, along with characteristic clinical findings confirmed the diagnosis of SLE. Every patient with a positive LE cell test had at least one other abnormal immunologic reaction demonstrated by laboratory tests. These included decreased complement (three patients), presence of antinuclear antibodies (three), positive Farr test (two), positive heterophile, positive complement fixation with nuclei, positive direct Coombs test, positive VDRL, positive STS and positive latex fixation (one patient each).

Splenectomy

Indications

Corticosteroids were first used in the treatment of SLE in 1949.[7] Nine of our ten patients were seen after this date. These nine patients underwent splenectomy either because high-dose steroids were ineffective in controlling the bleeding manifestations or because the steroid dosage required was associated with potentially serious side effects. Three of our patients underwent splenectomy because of inadequate clinical response to high-dose corticosteroids, and six underwent splenectomy because the dosage of steroids to

TABLE 2. *Non-hematologic Manifestations of SLE*

Manifestations	No. of Patients
Musculoskeletal (*e.g.* arthralgias)	6
Rash	6
GI (*e.g.* nausea, vomiting)	3
Nephritis	3
Recurring pneumonitis	2
Raynaud's *phenomenon*	2
Pleurisy	1

maintain adequate platelet count was unacceptably high. In our patients a course of steroids at least equivalent to prednisone 40 mg daily for four weeks was given before deciding upon splenectomy. No patient required emergency splenectomy for massive or intracranial hemorrhage. Patient 1 was seen in 1946, prior to the availability of corticosteroids, and underwent splenectomy as primary therapy.

Results

Splenectomy resulted in an immediate dramatic rise in platelet counts which reached a maximum after several days. An exception to this was patient 8 who died in the early postoperative period and is discussed subsequently. In addition, even patients who had a poor response when given corticosteroids had gratifying rises in platelet counts following splenectomy (patients 2 and 7) (Table 1).

Follow-up was obtained in nine of the ten patients for one year or until death ensued. One patient (5) was lost to follow-up. Two patients (20%) died postoperatively. Both these patients had severe and widespread SLE. Patient 8 died on the seventh postoperative day from overwhelming cytomegalovirus and mucormycosis pneumonia confirmed at autopsy. This patient preoperatively had lupus nephritis with a creatinine of 3 mg%, and a BUN of 70 mg%, as well as lupus of the central nervous system. She had also recently required bowel resection for small bowel infarction from vasculitis. Hypoxemia was noted on the first postsplenectomy day, and a down-hill course ensued. The last platelet count, performed on the fifth postoperative day, showed no change from the preoperative value. The reason for this is conjectural but may be related in part to the lethal infection, and to the fact that the patient was on high doses of drugs known to cause thrombocytopenia (Dilantin, penicillin, gentamicin). The other postoperative death (patient 7) also had significant lupus nephritis (creatinine 2.2 mg%; BUN 58 mg%). At the time of splenectomy, with a platelet count of 1000/mm³, an acute gangrenous appendicitis was discovered incidentally. Signs and symptoms, except for mild lower abdominal pain, had been masked preoperatively by massive doses of steroids given for the thrombocytopenia. Following splenectomy and appendectomy the patient died in renal failure with acute bacterial peritonitis.

Two other patients suffered postoperative complications. One (patient 10) developed a superficial wound infection, the other (patient 1), pneumonia. Both responded satisfactorily to treatment. Neither bleeding nor thromboembolism were problems in any patient postoperatively. Platelet transfusions were not required in our patients, but their immediate availability is advisable because postoperative hemorrhage may be a problem as in two cases reported by Bergin et al.[1]

Patient 2 died one year postoperatively from what was described as a cerebrovascular accident. At the time of her death she was not taking corticosteroids and her platelet count was 785,000/mm³. Therefore there were six remaining patients who received follow-ups from one to 30 years. None of these patients had subsequent thrombocytopenia requiring corticosteroid treatment. The results of follow-up are given in Table 1.

Pathologic Specimen

In four of the ten cases the spleen showed the "onion-skin lesions" which are characteristic of SLE, and consist of perivascular fibrosis around central and penicilliary arteries. Patient 8, who died from viral pneumonia, was found to have viral inclusions in her spleen consistent with cytomegalovirus. One spleen showed hemosiderosis and another showed myeloid change. The spleens weighed from 76 to 500 g with a mean of 243 g. Two spleens were enlarged by weight, and fell outside the normal weight range for the age of the patient (patient 1, 500 g: patient 10, 400 g).[9] Only one of these two spleens was palable on physical examination.

Case Report

A 32-year-old Caucasian woman (patient 10) was transferred to NYH-CMC for evaluation of possible splenectomy. She had a history of SLE with positive LE cell prep, and decreased serum complement. Five months prior to admission menorrhagia and purpuric skin lesions lead to the discovery of thrombocytopenia. Bone marrow aspiration showed megakaryocyte hyperplasia. Treatment with prednisone 50 mg daily resulted in a rise in platelet count to about 200,000/mm³, and a reversal of the clinical manifestations. Lowering the steroid dosage, however, was associated with relapse of the hematologic abnormality. Because of the necessity of continuing high-dose corticosteroids splenectomy was performed.

The platelet count rose to 498,000/mm³ on the eighth postoperative day. Although the course was complicated by a superficial staphylococcus aureus wound infection, the patient was well and free of steroid therapy with a platelet count of 300,000 a year later.

Comment

This patient had a prompt response to splenectomy performed because the dose of steroids required to maintain hematologic remission was prohibitive. In many ways this case is typical of those seen at NYH–CMC. Despite the depressed serum complement level, tests of kidney function were within normal range.

Thrombocytopenic purpura and its complications may be vexing problems in patients with SLE. Of our nine patients treated by splenectomy and receiving adequate follow-up, seven showed a good response with an adequate rise in platelet count and disappearance of clinical manifestations of thrombocytopenia. The remaining two patients died primarily as a result of complications of corticosteroid therapy and severe SLE. Thus, in selected patients splenectomy may be indicated for the treatment of SLE-associated thrombocytopenic purpura.

Discussion

Systemic lupus erythematosus is a chronic disease of unknown etiology which affects many organ systems individually or in combination. Characteristically these patients develop autoimmune phenomena including antinuclear, anticell, and anticytoplasmic antibodies. SLE is not a rare disease, as once thought, and, in fact, the rate of occurrence of recognized cases is increasing. It is now estimated that its prevalence is 500 cases per million population in the United States.[7]

The thrombocytopenia found in patients with SLE is probably an immunologic phenomenon related to the production of antiplatelet antibodies.[8] The spleen, the largest source of lymphoid tissue in the body, may be implicated either as a significant source of the production of antibodies or as a major sequestering site for sensitized platelets. Removal of the spleen might thus be expected to produce a satisfactory remission in the thrombocytopenia. The finding of increased or normal megakaryocytes in the bone marrow of our patients supports the concept of peripheral destruction of platelets rather than failure of production.

Symptoms of thrombocytopenic purpura due to SLE have been petechiae, ecchymoses, menorrhagia, epistaxis, hematuria, and bleeding gums. Platelet counts have been lower than 50,000/mm^3 and have been recorded as low as zero.

The thrombocytopenic purpura of SLE closely resembles idiopathic thrombocytopenic purpura (ITP). ITP also has as its characteristics a reduced peripheral platelet count, normal or increased megakaryocytes in the marrow, and similar clinical manifestations. The pathogenesis of ITP is likewise thought to be related to the formation of anti-platelet antibodies.[8] By definition, however, the term ITP is reserved for those cases in which there is no systemic disease, nor a history of ingestion of drugs capable of inducing thrombocytopenia. On the other hand, thrombocytopenic purpura occurring in association with SLE is termed secondary thrombocytopenic purpura.[6,14]

Historically, in fact, the relationship between ITP and SLE has been hotly debated. At one time the concept that ITP was often a prodrome of SLE, and that splenectomy was a factor in the dissemination of occult SLE had distinguished supporters.[4] Others, particularly Best and Darling,[2] have refuted this concept. Doan et al.[6] showed that SLE occurs in two per cent of patients with thrombocytopenic purpura, and in only 1.2% of ITP patients following splenectomy. It is now widely held that splenectomy has no adverse effect upon the natural history of SLE. In fact, some considerations might lead to the opposite conclusion. Splenectomy, by removing a major site of antibody formation in the body, might affect positively a disease which is primarily one of auto-immunization. From our series no definite conclusions can be drawn concerning this point since SLE ordinarily has a remitting, relapsing course and any improvement in a small number of patients could be attributed to the natural course of the disease process itself. Splenectomy, however, did not seem to have an adverse effect on the SLE in our series.

Treatment of thrombocytopenic purpura in SLE should start with a trial of high dose steroids for three to four weeks. Splenectomy should be reserved for those patients in whom steroid therapy is ineffective, or in whom continuing high dose steroids is necessary to maintain adequate platelet counts. In these circumstances splenectomy is indicated and had been shown to be therapeutic. On the other hand, patients who represent a high surgical risk because of widespread lupus or other medical problems should be maintained on corticosteroids. Similarly, patients with thrombocytopenic purpura who will require long-term high-dose steroids anyway because of another complication of SLE, such as lupus nephritis or myocarditis, should not undergo splenectomy if the corticosteroids bring the platelet count into satisfactory range. In these situations where it is elected to continue steroid therapy the use of vincristine, cytoxan or azathiaprine may be useful adjuncts in order to lessen steroid induced complications. Selective embolization of the splenic artery to reduce splenic function is currently being evaluated in some centers and may become an alternative to splenectomy in certain patients.[3] We, however, have had no experience with this particular method. The long-term effect of splenectomy, in terms of infection, on patients with SLE is unresolved at present, but future studies should prove enlightening. We advise against maintaining good risk patients on high dose steroids for a prolonged period of time in the vain hope of avoiding an operation. This attitude subjects these patients to complications of steroid therapy that are worse than SLE itself if the major clinical problem is thrombocytopenia.

References

1. Bergin, J. J., Zuck, F. F. and Miller, R. E.: Compelling Splenectomy In Medically Comprised Patients. Ann. Surg. 178:761, 1973.
2. Best, W. R. and Darling, D. R.: A Critical Look At The Splenectomy-SLE Controversy. Med. Clin. North Am. 46:19, 1962.
3. Chuang, V. P. and Reuter, S. R.: Experimental Diminution Of Splenic Function By Selective Embolization Of The Splenic Artery. Surg. Gynecol. Obstet. 140:715–720, 1975.
4. Dameshek, W.: Controversy In Idiopathic Thrombocytopenic Purpura. JAMA, 173:1025, 1960.
5. Dameshek, H. L. and Ellis, L. D.: Hematologic Indications For Splenectomy. Surg. Clin. North Am., 55(2), 253, 1975.
6. Doan, C. A., Bouroncle, B. A. and Wiseman, B. K.: Idiopathic And Secondary Thrombocytopenic Purpura: Clinical Study And Evaluation of 381 Cases Over A Period Of 28 Years. Ann. Int. Med. 53:861, 1960.
7. Fries, J. F. and Holman, H. R.: Systemic Lupus Erythematosus: A Clinical Analysis. Philadelphia, W. B. Saunders Co., 1975, pp. 44–79.
8. Karpatkin, S. and Siskind, G.: In Vitro Detection Of Platelet Antibody In Patients With Idiopathic Thrombocytopenic Purpura And Systemic Lupus Erythematosus. Blood 33:795, 1969.
9. Krumbhaar, E. B. and Lippincott, S. W.: The Post Mortem Weight Of The "Normal" Human Spleen At Different Ages. Am. J. Med Sci., 197:344, 1939.
10. Philpitt, G. W. and Ballinger, W. F.: The Spleen, In Sabiston, DC (ed): Textbook Of Surgery. Philadelphia, W. B. Saunders Co., 1972, P.1122.
11. Sandusky, W. R., Leavell, S. and Benjamin, B. I.: Splenectomy Indications And Results In Hematologic Disorders. Ann. Surg. 159:695, 1964.
12. Schur, P. H.: Systemic Lupus Erythematosus, *In* Beeson, P. B., McDermott, W. (eds.) Textbook Of Medicine. Philadelphia, W. B. Saunders Co., 1975.
13. Schwartz, S. I.: Spleen, *In* Schwartz, S. I. (ed): Principles Of Surgery. New York, McGraw-Hill Book Co., 1974, P.1289.
14. Schwartz, S. I., Bernard, R. P., Adams, J. T. and Bauman, A. W.: Splenectomy For Hematologic Disorders. Arch Surg. 101:338, 1970.

FERGUSON'S SURGERY OF THE AMBULATORY PATIENT

Edited by Mark W. Wolcott, M.D.

Here is the *fifth edition* of a clinically oriented volume providing a clear "how to do it" approach covering most of the simpler conditions of the skin, bones, joints, and bursa in a succinct, easy-to-follow style.

For this revision the material on fracture and on soft tissue is consolidated, making reference to this information much easier. New chapters include *Cryosurgery*, and *Shunts and Fistulas for Hemodialysis. Ambulatory Gynecology* is a new subject to this edition, and the chapter on *Snake Bite and Insect Bites* is totally rewritten and enlarged.

This popular volume has served as a guide to the doctor in the subject of "minor surgery" for more than thirty years.

Surgery, Gynecology and Obstetrics said of the previous edition: "This book covers the field . . . admirably, and it is an invaluable work for every surgeon who treats patients in his office."

554 pages / 408 illustrations / 5th Edition, 1974
Flexible binding, $27.00

PERIPHERAL VASCULAR SURGERY

Edited by Martin Birnstingl, M.D., F.R.C.S.

This work, a contribution of recognized authorities writing from their own surgical experience, is a classic blend of basic scientific knowledge and advanced surgical techniques. Chapters range from *Hyperlipoproteinaemia and Vascular Disease* to *Micro Vascular Surgery*.

Full attention is given to *anatomy and physiology, etiology, pathology, signs and symptoms, laboratory tests* and such sophisticated modalities as *ultrasound flow detectors, angiography, phlebography, differential diagnosis, treatment* and *prognosis*.

The authors provide critical assessment of long-term results of arterial reconstruction in various anatomical situations, based on their appreciation of current vascular surgery.

". . . a pleasure to read. It is of particular value to the surgeon interested in vascular disease, but it is also an excellent review book for all interested in newer trends in vascular surgery."—*The Lancet.*

447 pages / 143 illustrations / 1973 / $21.00

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ■ Philadelphia, Pa. 19105

Please send me:

☐ FERGUSON'S SURGERY OF THE AMBULATORY PATIENT $27.00

☐ PERIPHERAL VASCULAR SURGERY $21.00

Name ______________________________

Address ______________________________

City ______________ State ______________ Zip ______________

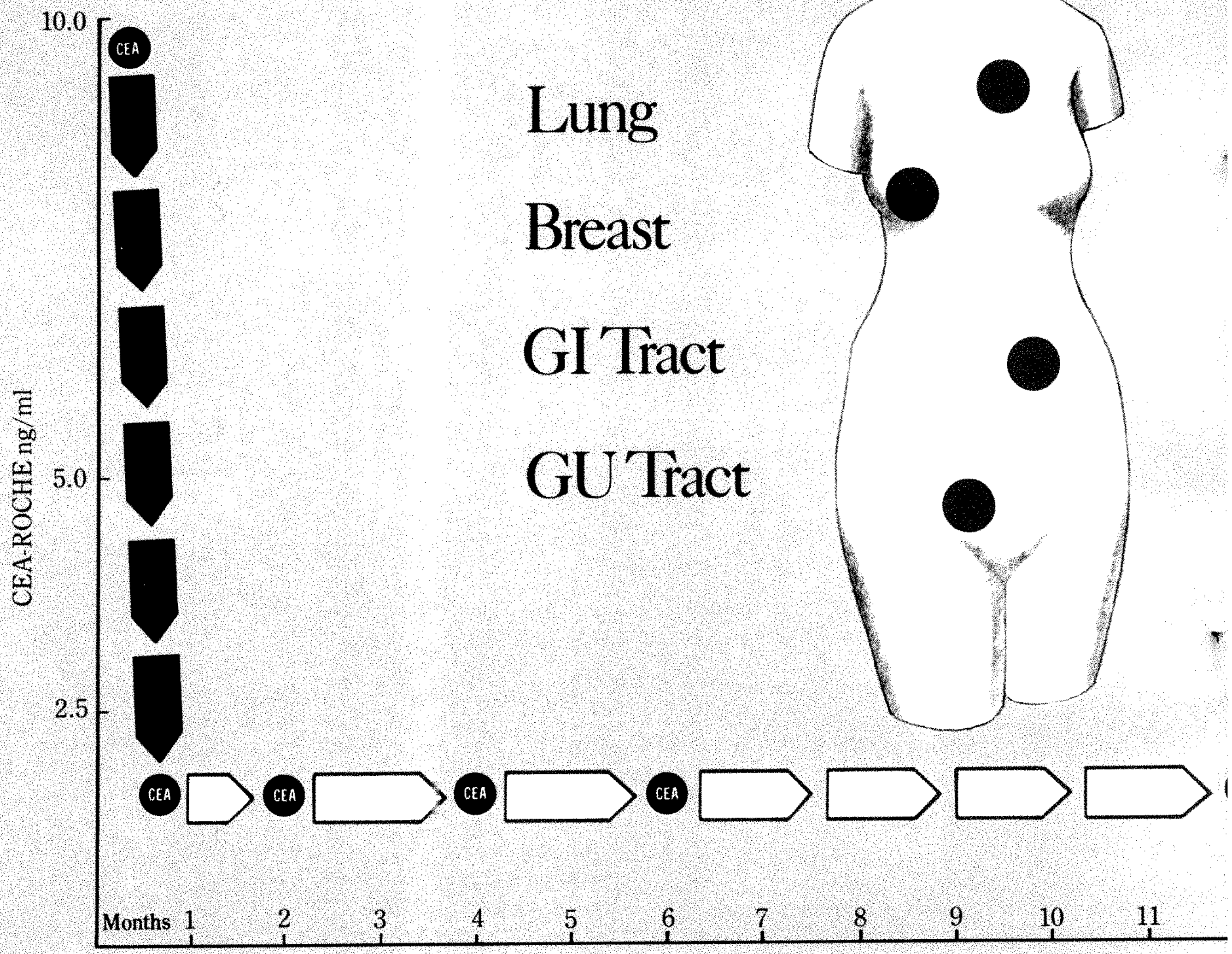
☐ Payment enclosed ☐ Charge and bill me
(Save postage & handling)

AS 1/78

Also available at your medical bookstore

In cancer management

periodic CEA-ROCHE assays may detect recurrence of disease months before other clinical signs are evident



Therapeutic Response Curve

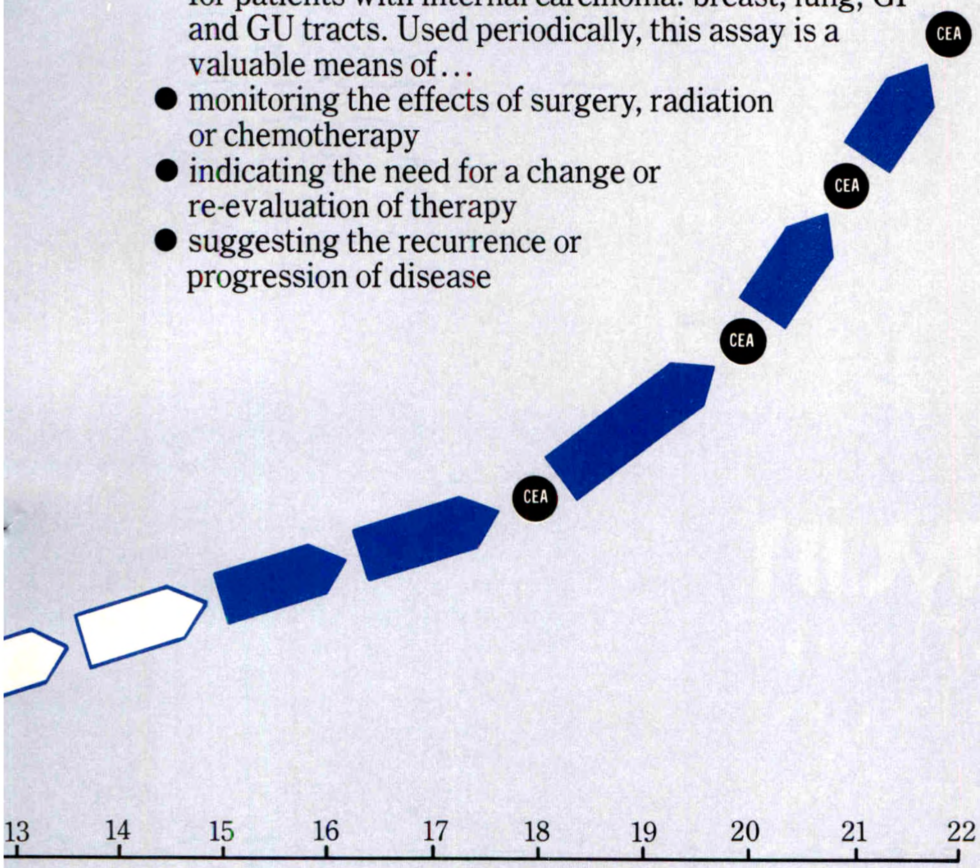
CEA-ROCHE, when used as a biological marker for following the cancer patient's response to therapy, should be employed periodically to determine a trend. The first test (preferably taken prior to beginning treatment) is used as a baseline against which subsequent tests are measured. Investigators have recommended that assays be run every 3-4 weeks during periods of active therapy, then once every 1-2 months for the first six months after completion of therapy; and finally, every 6-12 months as part of the long-term follow-up.

Results of periodic CEA-ROCHE assays have been found to closely mirror clinical response to therapy. Effective therapy normally results in a drop in an elevated CEA titer to levels below 2.5 ng/ml. Conversely, CEA titers usually remain elevated in the presence of refractory disease or when therapy is unsuccessful.

CEA-ROCHE
Carcinoembryonic Antigen assay
a valuable adjunct to other laboratory tests for monitoring the cancer patient's status

Four years of extensive clinical use have shown CEA-ROCHE to be an important part of the total management program for patients with internal carcinoma: breast, lung, GI and GU tracts. Used periodically, this assay is a valuable means of…

- monitoring the effects of surgery, radiation or chemotherapy
- indicating the need for a change or re-evaluation of therapy
- suggesting the recurrence or progression of disease



Progression/Recurrence Curve

The importance of periodic CEA-ROCHE assays for the prompt recognition of tumor progression/recurrence has been found to be "crucial in the clinical follow-up of these [cancer] patients." The same report also showed that progressively rising titer levels often preceded actual clinical relapse by weeks to months.*

CEA-ROCHE
may be ordered from
- **Roche Clinical Laboratories, Inc.**
  Five Johnson Drive
  Raritan, New Jersey 08869
  (201) 526-2400
  800-631-5250
- Major hospital and private laboratories

ROCHE

Complete and mail the following coupon to W-6

Professional Services Department
Roche Laboratories
340 Kingsland Street
Nutley, New Jersey 07110
(201) 235-4873

I am interested in knowing more about the use of CEA-ROCHE as a management aid in patients with

☐ Breast cancer
☐ Lung cancer
☐ GI cancer
☐ GU cancer

Please send me some of the current reprints in the area(s) I have indicated above.

Name

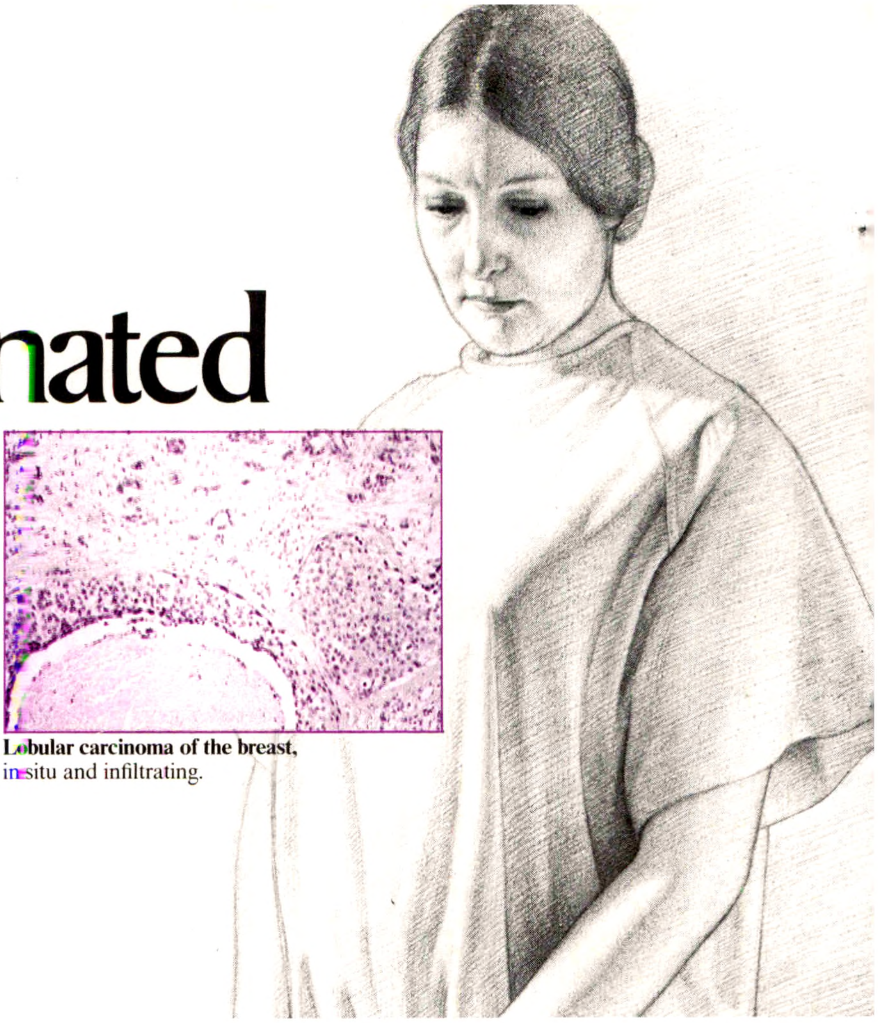
Specialty/Title

Hospital/Laboratory

Address

City State Zip

Disseminated Breast Cancer



Lobular carcinoma of the breast,
in situ and infiltrating.

One of a number of malignancies in which Adriamycin is of importance.

Adriamycin™
(doxorubicin hydrochloride) for Injection

FOR INTRAVENOUS USE ONLY
10 mg and 50 mg vials

In addition to advanced metastatic cancer of the breast, other disseminated neoplastic conditions have responded to Adriamycin and include: acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, osteogenic and soft tissue sarcoma, neuroblastoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, lymphoma of both Hodgkin's and non-Hodgkin's type, and bronchogenic lung carcinoma in which the small cell histologic type is the most responsive compared to other cell types. Adriamycin should be administered only under the direction of specialists qualified in the administration of such drugs.

Severe local tissue necrosis will occur if there is extravasation during administration.

Severe irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m^2. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.

The incidence of bone marrow depression is high. Hematopoietic toxicity may limit dosage.

In patients with impaired hepatic function, dosage should be reduced.

For information on the use of Adriamycin, call collect (302) 575-7830.

Adria™
LABORATORIES INC.

For complete prescribing information, please see the following page.

Adria Laboratories Inc.

ADRIAMYCIN™ (doxorubicin hydrochloride) for Injection
FOR INTRAVENOUS USE ONLY

WARNINGS

1. Severe local tissue necrosis will occur if there is extravasation during administration. Adriamycin must not be given by the intramuscular or subcutaneous route.
2. Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m^2. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.
3. Dosage should be reduced in patients with impaired hepatic function.
4. Severe myelosuppression may occur.
5. Adriamycin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. It is supplied in the hydrochloride form as a freeze-dried powder containing lactose.

CLINICAL PHARMACOLOGY

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity in rabbits, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetic studies show the intravenous administration of normal or radiolabeled Adriamycin (doxorubicin hydrochloride) for Injection is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40-50% of the administered dose being recovered in the bile or the feces in seven days. Impairment of liver function results in slower excretion, and, consequently, increased retention and accumulation in plasma and tissues. Adriamycin does not cross the blood brain barrier.

INDICATIONS

Adriamycin has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, lymphomas of both Hodgkin and non-Hodgkin types and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types. A number of other solid tumors have also shown some responsiveness but in numbers too limited to justify specific recommendation. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinoma, brain tumors and metastases to the Central Nervous System not to be significantly responsive to Adriamycin therapy.

CONTRAINDICATIONS

Adriamycin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy. Conclusive data are not available on pre-existing heart disease as a co-factor of increased risk of Adriamycin induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended to start Adriamycin in such cases. Adriamycin treatment is contraindicated in patients who received previous treatment with complete cumulative doses of Adriamycin and daunorubicin.

WARNINGS

Special attention must be given to the cardiac toxicity exhibited by Adriamycin. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m^2. This limit appears to be lower (400 mg/m^2) in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The total dose of Adriamycin administered to the individual patient should also take into account a previous or concomitant therapy with related compounds such as daunorubicin. Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of Adriamycin therapy.

Cardiac failure is often not favorably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. Baseline EKG and periodic follow-up EKG during, and immediately after, active drug therapy is an advisable precaution. Transient EKG changes, such as T-wave flattening, S-T depression, and arrhythmias are presently not considered indications for suspension of Adriamycin therapy. A persistent reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematological monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10-14 days after treatment with recovery usually occurring by the 21st day. White blood cell counts as low as $1000/mm^3$ are to be expected during treatment with appropriate doses of Adriamycin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of Adriamycin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

It has been reported that Adriamycin may enhance the severity of the toxicity of anticancer therapies such as exacerbation of cyclophosphamide induced hemorrhagic cystitis, mucositis induced by radiotherapy, and hepatotoxicity of 6-mercaptopurine.

Toxicity to recommended doses of Adriamycin is enhanced by hepatic impairment; therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, bilirubin, and BSP. (See Dosage and Administration.)

On intravenous administration of Adriamycin, a stinging or burning sensation signifies a small degree of extravasation and even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein.

PRECAUTIONS

Initial treatment with Adriamycin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalized at least during the first phase of the treatment.

There is no adequate information on whether this drug may adversely effect fertility in human males or females, or have a teratogenic potential or other adverse effects on the fetus. Experimental teratology studies, though not showing a definite increase in specific or nonspecific malformations indicate a moderate interference with the viability of embryos and fetuses. Adriamycin has been shown to be abortifacient when given in high doses to rabbits. Therefore the benefits to the pregnant patient should be weighed against the potential toxicity to fetus and embryo. Adriamycin and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Like other cytotoxic drugs, Adriamycin may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Adriamycin imparts a red coloration to the urine for 1-2 days after administration and patients should be advised to expect this during active therapy.

Adriamycin is not an anti-microbial agent.

ADVERSE REACTIONS

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity (see Warnings). Other reactions reported are:

Cutaneous - Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily, occurs in children in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with Adriamycin administration.

Gastrointestinal - Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5-10 days after administration. The effect may be severe leading to ulceration and represent a site of origin for severe infections. The incidence and severity of mucositis is greater with the 3 successive daily dosage regimen. Anorexia and diarrhea have been occasionally reported.

Vascular - Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local - Severe cellulitis, vesication and tissue necrosis will occur if Adriamycin is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported.

Hypersensitivity - Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other - Conjunctivitis and lacrimation occur rarely.

DOSAGE AND ADMINISTRATION

Care in the administration of Adriamycin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reaction such as urticaria and erythematous streaking.

The recommended dosage schedule is 60-75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is 30 mg/m^2 on each of three successive days repeated every 4 weeks. Adriamycin dosage must be reduced if hepatic function is impaired according to the following table:

Serum Bilirubin Levels	BSP Retention	Recommended Dose
1.2-3.0 mg %	9-15%	½ normal dose
> 3 mg %	> 15%	¼ normal dose

Preparation of Solution: Adriamycin 10 mg vials and 50 mg vials should be reconstituted with Sodium Chloride Injection U.S.P. 5 ml and 25 ml respectively, to give a final concentration of 2 mg/ml of doxorubicin hydrochloride.

Both powder and solution must be handled with care. If Adriamycin powder or solution contacts the skin or mucosae, wash thoroughly with soap and water.

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration (4-10°C). It should be protected from exposure to sunlight and any unused solution should be discarded.

It is recommended that Adriamycin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection U.S.P. or 5% Dextrose Injection U.S.P. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. However the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein.

Adriamycin should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that Adriamycin be mixed with other drugs.

Adriamycin has been used in combination with other approved chemotherapeutic agents. Though evidence is available that at least in some types of neoplastic disease combination chemotherapy is superior to single agents, the benefits and risks of such therapy have not yet been fully elucidated.

HOW SUPPLIED

ADRIAMYCIN™ (doxorubicin hydrochloride) for Injection is available in two sizes:

10 mg - Each rubber disc-capped vial contains 10 mg of doxorubicin HCl and 50 mg of lactose U.S.P. as a sterile red-orange lyophilized powder. Packaged and supplied in 10-vial cartons NDC 38242-874-10.

50 mg - Each rubber disc-capped vial contains 50 mg of doxorubicin HCl and 250 mg of lactose U.S.P. as a sterile red-orange lyophilized powder. Packaged and supplied in a single vial carton NDC 38242-875-50.

03701A M 8740102-1A 80076

Adria™
Distributed by Adria Laboratories
1105 Market Street
Wilmington, Delaware 19899
Manufactured by: Farmitalia S.p.A., Italy.

NEW YORK UNIVERSITY
POST-GRADUATE MEDICAL SCHOOL
announces a postgraduate seminar
in
surgery

CLINICAL SURGERY 1978

Course Directors: Drs. Frank C. Spencer, Kenneth Eng,
Joseph N. Cunningham, Jr.

Monday to Friday — Fee: $385
April 3-7, 1978 — 8:00 AM to 5:00 PM

This course is designed to present resent advances in the pathophysiology, diagnosis, and treatment of surgical disease. Current therapy and practice in abdominal, vascular, trauma and tumor surgery of concern to the general surgeon and supportive care of the surgical patient are presented through lectures, panel discussions, audiovisual aids and annotated notes and references. Ample time for questions from participants as well as attendance at selected conferences and operations are arranged dependent on demand. A special feature of the course is a laboratory demonstration of monitory techniques.

Accreditation: AMA Category I credit hours

For information, write or phone: Registration Department, NYU Post-Graduate Medical School, 550 First Avenue, NYC, NY 10016; 212-679-3200, Ext. 4038.

Special Note: tuition includes syllabus, continental breakfast, refreshments, luncheons.

AN700

Preregistration Form—Please type or print
Return to: NYUPGMS, Registration Dept.
550 First Ave., NYC, NY 10016
212-679-3200, Ext. 4038

Name ____________ Phone ________

Address ____________

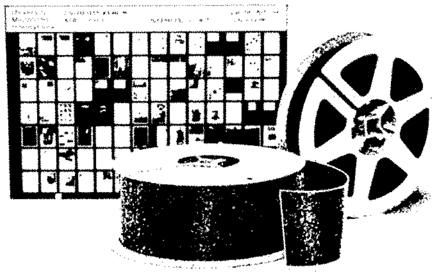
____

Enclosed:
$385
$289 (alumni, former residents and fellows NYU School of Medicine; physicians in training; active military personnel; members, National Health Service Corps. (Certification of Chief of Service needed if in training)

Date ________ Signature ________

Please send further information ___ yes

this publication is available in microform



Please send me additional information.

University Microfilms International

300 North Zeeb Road
Dept. P.R.
Ann Arbor, MI 48106
U.S.A.

18 Bedford Row
Dept. P.R.
London, WC1R 4EJ
England

Name ____________
Institution ____________
Street ____________
City ____________
State ____________ Zip ________

FACULTY POSITIONS

College of Medicine, King Faisal University
Dammam, Saudi Arabia

Applications invited from qualified men and women in General Surgery. American Board certification in surgery (or equivalent in Canada or Great Britain) plus teaching experience required. Language of instruction is English. Positions available in September 1978; interviews scheduled with the Dean in the United States early in 1978.

Salary ranges: (Given monthly in Saudi Riyals followed by approximate annual equivalent in U.S. dollars)

	Academic Salary	+	*Clinical Bonus of 50%*	=	*Total Approximate yearly dollars*
Professor:	SR 6,000-6,600		SR 3,000-3,300		($30,500-33,500)
Assoc. Prof.:	SR 4,800-5,800		SR 2,400-2,900		($24,400-29,400)
Assist. Prof.:	SR 3,600-4,600		SR 1,800-2,300		($18,300-23,400)

Benefits include free furnished accommodations and annual leave with travel allowance to country of origin.

No Saudi income tax is imposed.

Send curriculum vitae and references with addresses and telephone numbers to:

Mohammed T. Altorki, M.D., MRCP
Dean of the Medical Faculty
King Faisal University
c/o Saudi Arabian Educational Mission
2223 West Loop South, Suite 400
Houston, Texas 77027

Specify dates of teaching appointments and availability.

Dome-Paste® Bandage

Modified Unna's Boot

Encourages healing of skin lesions...
contributes to patient's comfort

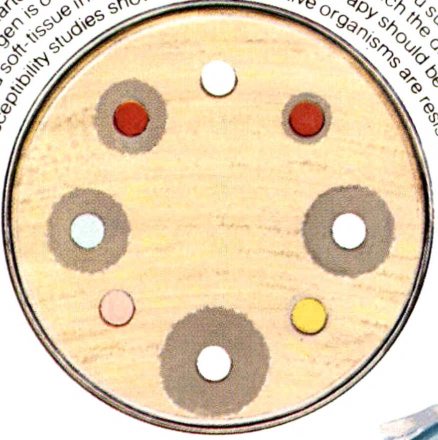
Now a new 3-inch width... easy application for smaller limbs, fewer wrinkling problems than with fraying bandages, greater economy.

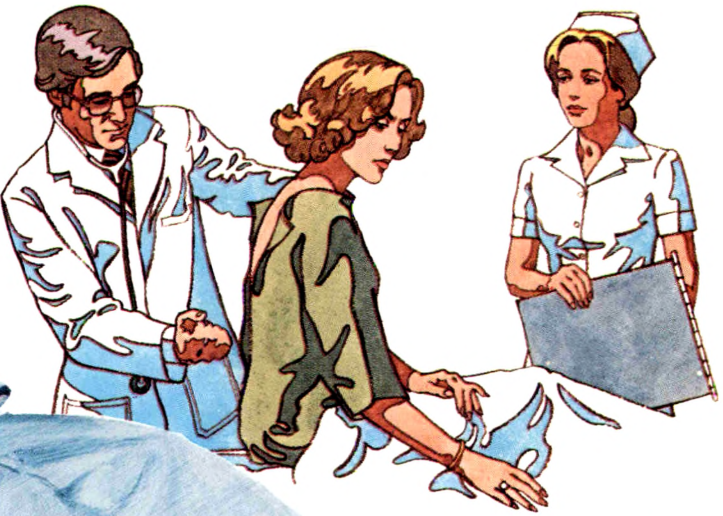
☐ Also in standard 4-inch width with nonraveling, thread-locked edges.
☐ Both sizes in 10-yard rolls, neutral-colored, rayon-reinforced for strength.
☐ Uniformly impregnated with zinc oxide, gelatin, calamine.
☐ Each roll sealed in a polyethylene bag to preserve freshness.
☐ Always ready for immediate use.

DOM-1306R2

Dome Laboratories
Division Miles Laboratories Inc MILES
West Haven Connecticut 06516 USA

Appropriate cultures should be taken, but Keflin® (cephalothin sodium, Lilly) may be started before susceptibility results are obtained if you suspect the causative pathogen is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections.* Other antibiotic therapy should be instituted if susceptibility studies show that the causative organisms are resistant.

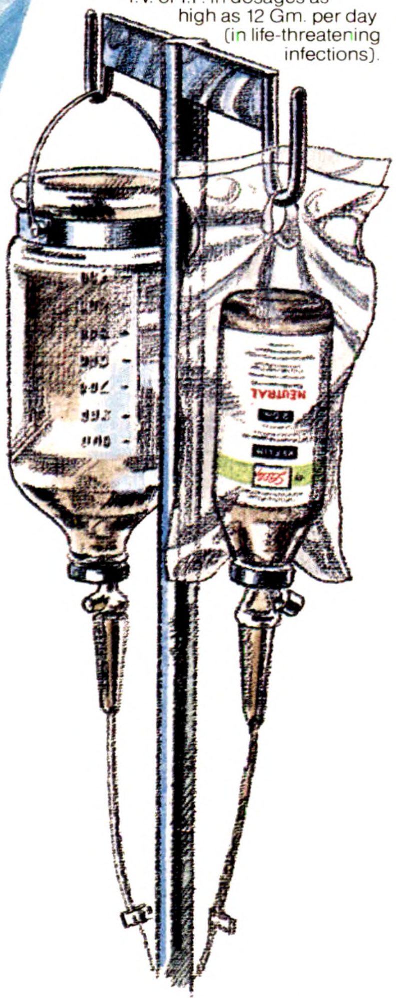




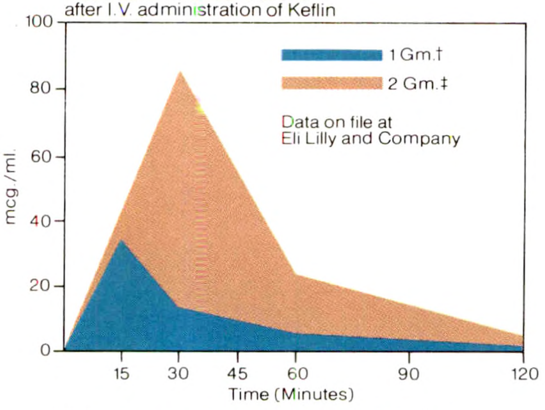
In the immunosuppressed patient, usual clinical signs and symptoms of infection may be missing or not clear. Hence, diagnosis and initiation of proper therapy become most urgent.

An initial loading dose of 1 to 2 Gm. of Keflin may be given regardless of the patient's renal status. Patients with impaired renal function should be placed on a reduced dosage schedule. Usual doses in such individuals may result in excessive serum concentrations.

Keflin may be administered I.V. or I.P. in dosages as high as 12 Gm. per day (in life-threatening infections).



Mean serum concentrations after I.V. administration of Keflin



† Administered to six patients by rapid I.V. infusion.
‡ Administered to ten patients over a thirty-minute period.

Please see opposite page for summary of prescribing information.

---

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

In serious skin and soft-tissue infections*

OFTEN USEFUL WHEN MOST NEEDED

As you know, skin and soft-tissue infections,* including peritonitis, may progress with alarming rapidity in patients with impaired host defenses...even to the point of becoming irreversible. Keflin can often be useful before the infection becomes irreversible...exactly when it is most needed.

Eleven years after its introduction, Keflin continues to be effective against most strains of gram-positive and gram-negative organisms commonly implicated in serious skin and soft-tissue infections.* Therefore, when you suspect that the pathogen involved is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections,* you may begin therapy with Keflin even while results of susceptibility studies are pending...and thus save precious hours for the patient. Keflin may be administered to infants and to patients with reduced renal function.

Keflin should be given cautiously to penicillin-sensitive patients.

It is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

* Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Keflin® 2 Gm.† in 100-ml. ampoule

cephalothin sodium

Neutral

for Injection

†Equivalent to cephalothin

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin* (cephalothin sodium, Lilly), Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

- Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*
- Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

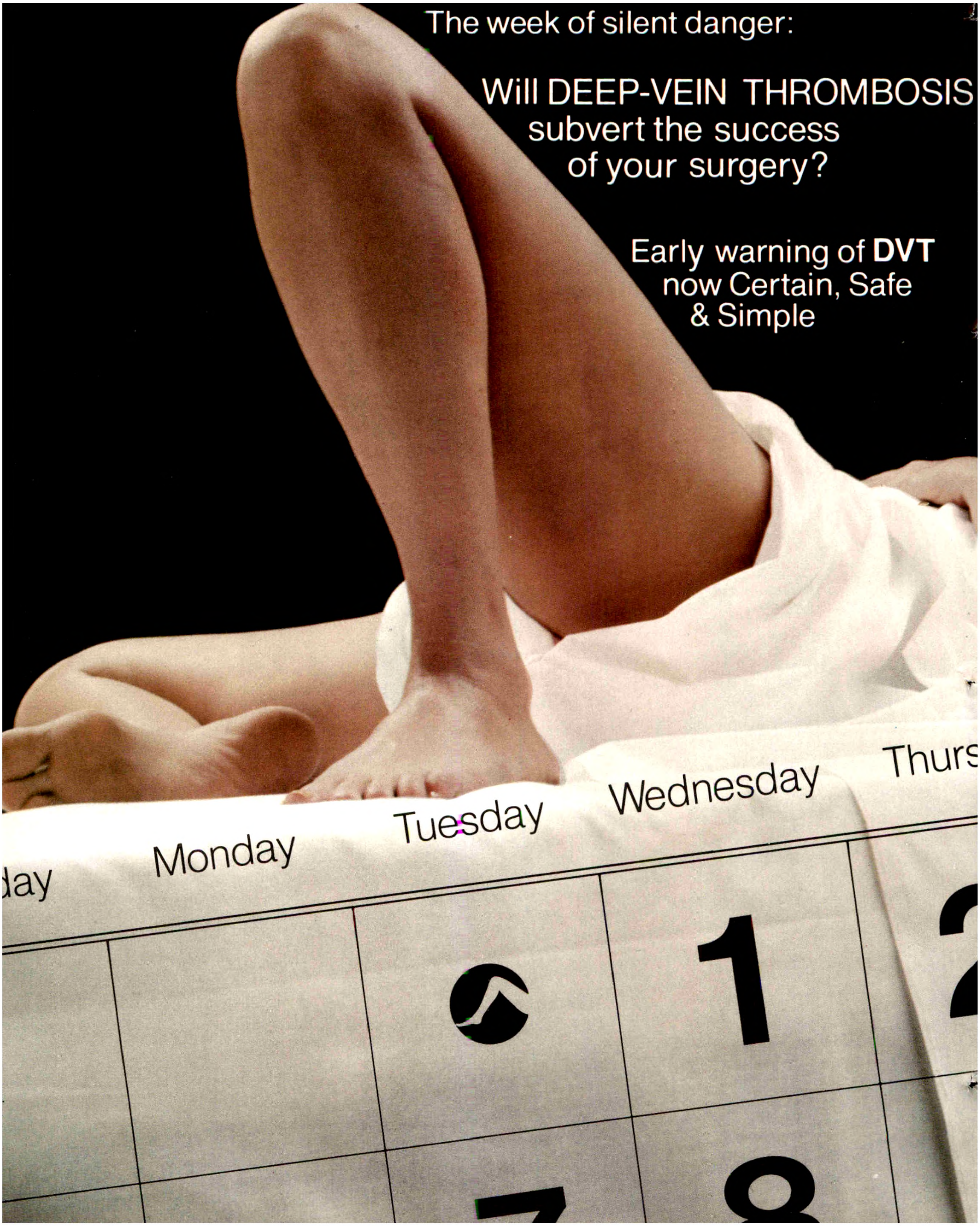
If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape* (urine sugar analysis paper, Lilly).

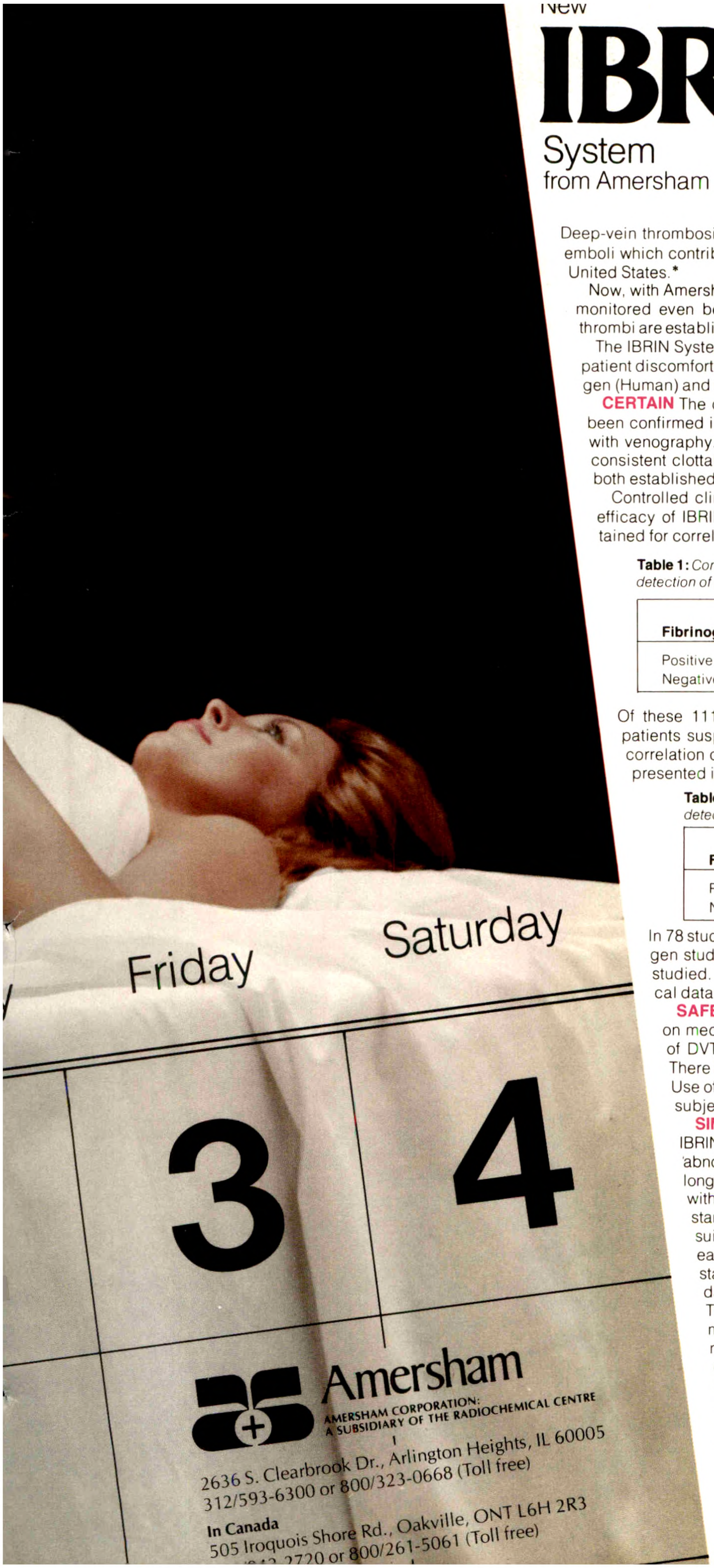
Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [111475S]

Additional information available to the profession on request.

Lilly

Eli Lilly and Company
Indianapolis, Indiana 46206


The week of silent danger:
Will DEEP-VEIN THROMBOSIS subvert the success of your surgery?
Early warning of **DVT** now Certain, Safe & Simple
day
Monday
Tuesday
Wednesday
Thurs
1
2
7
8



Amersham
AMERSHAM CORPORATION:
A SUBSIDIARY OF THE RADIOCHEMICAL CENTRE
2636 S. Clearbrook Dr., Arlington Heights, IL 60005
312/593-6300 or 800/323-0668 (Toll free)

In Canada
505 Iroquois Shore Rd., Oakville, ONT L6H 2R3
2720 or 800/261-5061 (Toll free)

New IBRIN System
from Amersham

IBRIN®
Radionuclide-Labeled
(^{125}I) Fibrinogen (Human)
IBRINITOR™
Portable Radioisotope Monitor

Deep-vein thrombosis (DVT) is thought to cause nearly 95% of the pulmonar emboli which contribute to over 50,000 post-operative deaths each year in th United States.*

Now, with Amersham's new IBRIN System, DVT can be detected and serial monitored even before any clinical symptoms are manifest...whether th thrombi are established or forming.

The IBRIN System is highly accurate, safe and easy to use, and minimize patient discomfort. It consists of IBRIN, a Radionuclide-Labeled (^{125}I) Fibrinogen (Human) and the IBRINITOR, a portable radioisotope monitor.

CERTAIN The diagnostic accuracy of IBRIN in the detection of DVT ha been confirmed in more than 100 studies which showed a 92% correlatio with venography. IBRIN actively participates in thrombus physiology; it consistent clottability insures bioactivity and allows accurate detection o both established and lysing thrombi.

Controlled clinical studies were conducted to establish the safety an efficacy of IBRIN. In 111 initially reported studies, venograms were obtained for correlation with the fibrinogen study results. (Table 1.)

Table 1: *Correlation of fibrinogen study with venogram for the detection of deep vein thrombosis in 111 cases.†*

Fibrinogen Results	Venogram Results	
	Positive	**Negative**
Positive 27	24	3
Negative 84	6	78

Of these 111 studies, 66 were performed as diagnostic studies o patients suspected of having established deep vein thrombosis. Th correlation of the fibrinogen study and venography in these studies i presented in Table 2.

Table 2: *Correlation of fibrinogen study with venograms for the detection of established deep vein thrombosis in 66 cases.†*

Fibrinogen Results	Venogram Results	
	Positive	**Negative**
Positive 17	16	1
Negative 49	4	45

In 78 studies without venogram correlation, the results of the fibrinogen study were positive in 17% and negative in 83% of the case studied. These test results were consistent with all available clinical data on these patients.

SAFE DVT monitoring with the IBRIN System can be performe on medical, surgical and orthopedic patients. The IBRIN Systen of DVT detection is easily performed at the patient's bedside There is no need to move the patient to a special procedural area Use of the IBRIN System for detection of DVT reduces the need t subject the patient to the risks of radiopaque venography.

SIMPLE The patient is intravenously injected with 100 μCi c IBRIN. Monitoring can begin within three hours after injection an abnormal results can be confirmed within 24 hours. IBRIN has long *in vivo* half-life, permitting monitoring up to seven day without additional injections. Serial monitoring allows for constant updating of the patient's status. The IBRINITOR is ideall suited for monitoring large numbers of patients quickly an easily. The electronic design assures reliable accumulation o statistically valid data and eliminates most operator error. data printout insures ease and accuracy of data collection These, plus many other design features of the IBRINITOR make it a dramatic improvement in DVT detection an monitoring. The IBRIN System is a complete mode of DV detection that minimizes the need for venography and contrast dyes. Accurate results are obtained with fewer complications and minimum patient discomfort.

Contact your Nuclear Medicine Department for detail on how the IBRIN System can benefit your post-surgica patients.

---

*Kakkar, V.V. "Deep Vein Thrombosis Detection and Prevention," *Circulation*, Volume 51, January 1975.
†Write or Phone for Complete Information.

See following page for brief summary of package insert

C77711

The
IBRIN
System

IBRIN™
Radionuclide-Labeled (^{125}I) Fibrinogen (Human)
IBRINITOR™
Portable Radioisotope Monitor

INDICATIONS
IBRIN is indicated for use in prospective studies for the early detection and subsequent monitoring of developing deep-vein thrombosis and in diagnostic studies for the detection of established thrombosis in the legs.

A. The IBRIN [Radionuclide-Labeled (^{125}I) Fibrinogen (Human)] test is indicated in patients with signs and/or symptoms suggestive of deep-vein thrombosis with or without associated pulmonary embolism or in patients with pulmonary embolism, with or without evidence of peripheral deep-vein thrombosis. In patients with established, old or "inactive" thrombi, the test will be positive only if radionuclide-labeled fibrin deposition occurs in a sufficient quantity to allow detection. Its use is not contraindicated in patients on anticoagulants.

B. The IBRIN [Radionuclide-Labeled (^{125}I) Fibrinogen (Human)] test is indicated for the detection of thrombus formation in patients undergoing major orthopedic or other surgical procedures, myocardial infarction, pulmonary disease, malignant disease and other medical conditions known to predispose to thromboembolism.

CONTRAINDICATIONS
There are no known contraindications to the use of IBRIN. However, it should be noted that the iodides given to block the uptake of ^{125}I by the thyroid gland are contraindicated in patients with a known sensitivity to the iodides.

WARNINGS
This radiopharmaceutical should not be administered to patients under 18 years of age, to patients who are pregnant, or to patients who are lactating, unless the information to be gained outweighs the potential risk.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of child bearing capability should be performed during the first few (approximately 10) days following the onset of menses. Nursing mothers should substitute formula feeding after the administration of Fibrinogen ^{125}I.

Extraordinary precautions have been taken in the preparation of IBRIN [Radionuclide-Labeled (^{125}I) Fibrinogen (Human)] to eliminate the possible transmission of hepatitis. Nevertheless, the remote risk of hepatitis associated with the administration of Radionuclide-Labeled (^{125}I) Fibrinogen (Human) cannot be entirely eliminated. The finding of viral hepatitis in any patient up to six months after the administration of IBRIN should be reported to Amersham for further evaluation, since there are numerous possible sources of hepatitis infection.

PRECAUTIONS
Care should be taken to insure minimum radiation exposure to the patient, consistent with proper patient management, and to insure minimum radiation exposure to occupational workers.

This drug contains radioactive materials which must be handled only by qualified personnel in conformity with Nuclear Regulatory Commission, agreement state, or other appropriate government regulations. Care must be taken to avoid excessive exposure to its radiation. Shielding or equivalent radiation protective measures must be used.

This product is prepared from units of human plasma which have been tested using RIA methods and found non-reactive for Hepatitis B surface antigen. Approved detection methods are not sensitive enough to detect all infectious units of blood or all possible cases of hepatitis. However, IBRIN has been prepared from single donor plasma and has been injected into recipients without incidence of fibrinogen related Hepatitis B as evidenced by periodic physical examination and laboratory testing (liver profile, CBC, and Hepatitis B surface antigen and antibody by radioimmunoassay) of the recipients.

There are a number of clinical circumstances requiring consideration in the interpretation of the test results. (See complete Package Insert.)

Fibrinogen ^{125}I scanning should preferably be performed prior to venography if both procedures are contemplated, since venography may cause increases in count rate making interpretation of post-venography monitoring data difficult.

Adequate reproduction studies on animals have not been performed to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Radionuclide-Labeled (^{125}I) Fibrinogen (Human) should be used in pregnant women only when clearly needed.

ADVERSE REACTIONS
There has been no reported incidence of allergic or anaphylactic reactions following the intravenous administration of IBRIN.

Amersham
AMERSHAM CORPORATION:
A SUBSIDIARY OF THE RADIOCHEMICAL CENTRE
2636 S. Clearbrook Dr., Arlington Heights, IL 60005
312/593-6300 or 800/323-0668 (Toll free)

In Canada
505 Iroquois Shore Rd., Oakville, ONT L6H 2R3
416/842-2720 or 800/261-5061 (Toll free)

Quick Reference To Surgical Emergencies

■

Edited by Gerald W. Shaftan, M.D. and Bernard Gardner, M.D.

This handy manual, packed with clinical data in easy-to-use outline form, is designed for instant use in helping you evaluate the surgical emergency, make the diagnosis and carry out the indicated treatment.

Divided into two broad categories of traumatic and non-traumatic surgical emergencies the book systematically covers: Techniques of evaluating the patient and applying diagnostic criteria . . . Radiologic procedures that are necessary . . . Anesthesia considerations . . . Fluid and electrolyte replacement.

The patient evaluating techniques, diagnostic steps and surgical treatment are presented step-by-step with each individual entry numbered for simplicity.

Subject matter includes emergencies occurring in the areas of general, orthopaedic, neurologic, ophthalmic, thoracic, plastic, urologic, head and neck, and pediatric surgery.

All who are involved in surgical emergency treatment will appreciate this easy-to-use, time-saving manual.

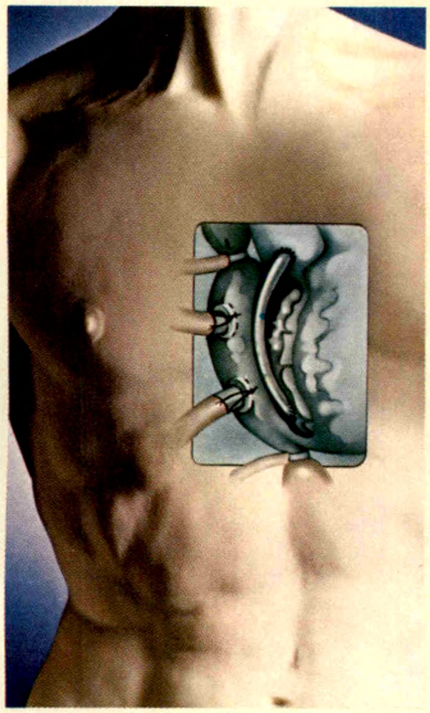
664 Pages • 50 Illustrations • 1974
Flexible Binding • $23.75

Lippincott
J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

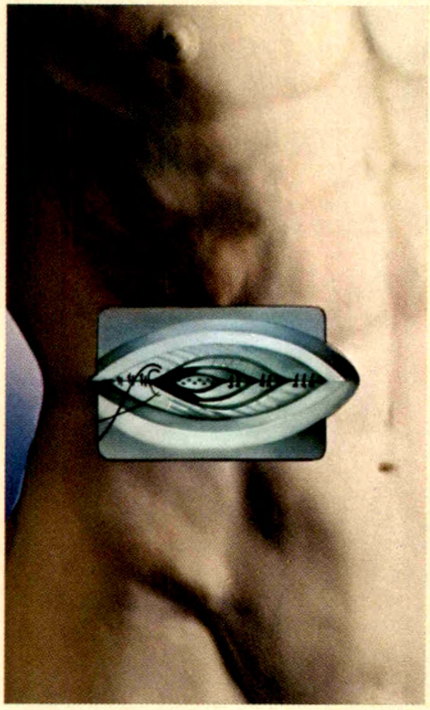
Please send me:
☐ QUICK REFERENCE TO SURGICAL EMERGENCIES $23.75
Name ____________________
Address ____________________
City ____________ State ________Zip ____
☐ Payment enclosed (Save postage & handling)
☐ Charge and bill me (Plus postage & handling)
Also available at your medical bookstore. AS 1/78

DAVIS+GECK

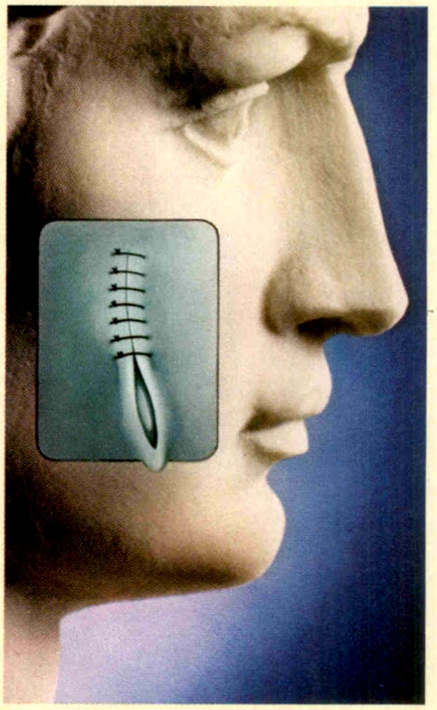
Smooth



Strong



Inert...



New SURGILENE®

polypropylene monofilament suture.

SURGILENE is so smooth and pliable, it glides through all kinds of tissue. This new polypropylene suture also ties easily and handles well. The result: fast, smooth procedures.

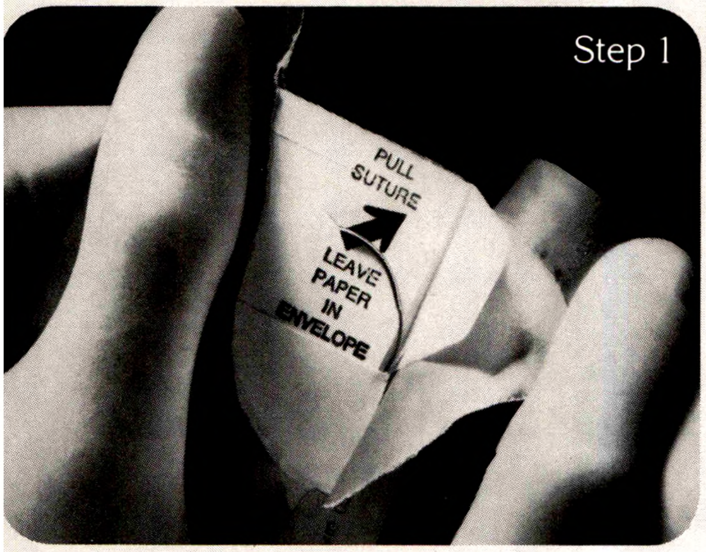
SURGILENE is inert, so scarring is minimal, complications few. And it's strong...with a flex life that's unexcelled by any other synthetic monofilament.

For your convenience, SURGILENE is available in our unique, time-saving DIRECT DISPENSING packages.

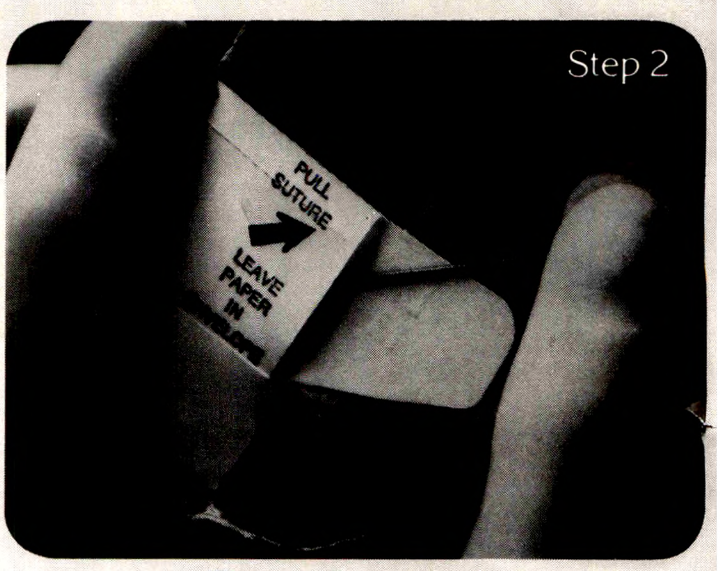
DG
DAVIS+GECK
American Cyanamid Company
Pearl River, N.Y. 10965

DAVIS+GECK

New SURGILENE®
polypropylene monofilament suture comes in unique, time-saving DIRECT DISPENSING packages.



Tear inner pack diagonally to expose suture.



Then, pull suture out.

SURGILENE® polypropylene monofilament suture
Complete Product Information

DESCRIPTION
SURGILENE *polypropylene* Suture, (clear or pigmented) is a sterile, isotactic crystalline stereoisomer of a linear hydrocarbon polymer having essentially no unsaturation. The pigmented suture contains Copper Phthalocyanine Blue.

ACTIONS
SURGILENE causes a minimal, transient, acute inflammatory reaction. This is followed by the formation of a microscopic layer of fibrous tissue around the suture. The suture is not absorbed nor is it subject to degradation or weakening by the action of tissue enzymes.

INDICATIONS
SURGILENE may be used wherever Nonabsorbable Surgical Suture, USP is recommended.

Because of its lack of adherence to tissue, SURGILENE is efficacious as a pull-out suture.

CONTRAINDICATIONS
There are no known contraindications.

WARNINGS
Studies to determine the safe and effective use of SURGILENE Suture in eye surgery have not been performed.

PRECAUTIONS
As with other synthetic sutures, knot security requires the standard surgical technic of flat and square ties, with additional throws if indicated by surgical circumstance and the experience of the operator.

There is an ongoing carcinogenicity study in rats, the results of which are not yet available.

ADVERSE REACTIONS
The most common adverse reaction noted during the clinical investigations with SURGILENE Suture was redness at the suture site, reported in up to 15% in some study populations. Edema and/or infection at the suture site has been noted in up to 8% in some study groups. Infrequent adverse reactions reported include suture extrusion and dehiscence (2 cases reported).

HOW SUPPLIED
Available in USP sizes, non-needled or affixed to the various DAVIS + GECK ATRAUMATIC® needles 10/0 thru 2 for pigmented sutures; 7/0 thru 2 for clear, in one dozen and three dozen packages.

Rev. 3/77

DG

The Effect of Jejunoileal Bypass on Bile Composition and the Formation of Biliary Calculi

LESLIE WISE, M.D., THEODORE STEIN, M.S.

In our series of 101 patients with small bowel bypass for morbid obesity, nine developed biliary calculi postoperatively during a mean follow-up period of 29.6 months. The development of gallstones depends in part on biliary cholesterol saturation and on the zeta potential of bile. In eight consecutive patients, the lithogenicity of bile was assessed by the methods of Small, Swell and Isaksson, which are dependent on cholesterol saturation. Postoperatively, the lithogenic score decreased in six and increased in two patients, one of which developed gallstones. Taurine bile salt conjugation tends to prevent aggregation of micelles by increasing the zeta potential. The biliary glycine/taurine ratio increased ($p < 0.05$) from 4.6 to 5.9 postoperatively. These results suggest that the increased incidence of cholelithiasis following small bowel bypass is not only due to a relative change in bile composition but is probably more significantly due to an increase in the biliary glycine/taurine ratio and a consequent decrease in the biliary zeta potential.

THE ASSOCIATION OF OBESITY and cholesterol cholelithiasis is fairly well documented. In individuals weighing more than 20% of their ideal weight, the incidence of cholesterol gallstone formation is two to three times more frequent than in ideal weight individuals.[7,10] Analysis of gallbladder and hepatic bile from morbidly obese subjects has demonstrated an increased occurrence of cholesterol supersaturation, which is associated with gallstone formation.[6] Cholesterol synthesis and turnover increases in obesity, the rate of synthesis being directly related to the excess adipose cellularity.

In recent years, the surgical treatment of obesity has become more frequent. The purpose of this study was to evaluate the effect of jejunoileal bypass on the incidence of gallstone formation, on the frequency of cholesterol saturation, and on biliary lipid composition in a group of morbidly obese patients.

From the Departments of Surgery, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York, The State University of New York (Stony Brook) and Washington University School of Medicine, St. Louis, Missouri

Materials and Methods

Jejunoileal bypass was performed by us in 101 patients with morbid obesity. The age of these patients at the time of bypass was 33.7 ± 9.0 years. The preoperative incidence of biliary calculi was 30.6%. The biliary composition was evaluated in eight of the 101 patients, who gave their informed consent to participate in this study. The physical characteristics of the eight patients are shown in Table 1.

All patients were admitted for evaluation to the Clinical Research Center at Barnes Hospital and were studied before and after the jejunoileal bypass. The bypass procedure performed by us is shown diagrammatically in Figure 1. In this procedure, 35 cm of the proximal part of the jejunum was anastomosed end-to-end to 10 cm of the terminal part of the ileum. The intervening segment of small bowel was excluded; the proximal end was closed and tethered to the mesojejunum to prevent intussusception, and the distal end was anastomosed end-to-side to the cecum.

Sample Collection

Diet was carefully planned by the dietary staff and all food was withdrawn at least 12 hours prior to sample collections. All medications which have been reported to influence bile metabolism were restricted. After an overnight fast, a gastroduodenal tube (Davol Inc., Providence, Rhode Island) was positioned into the second part of the duodenum. While gastric contents were evacuated by suction (Gumco vacuum pump), 1.0 Ivy dog unit/kg cholecystokinin (Karolinksa

---

Reprint requests: Leslie Wise, M.D., Department of Surgery, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. 11040.

Supported in part by NIH Grant #RR00036.

0003-4932-78-0100-0057-0075 © J.B. Lippincott Company

TABLE 1. *Physical Characteristics of Patients in Study*

Patient No.	Age, Yr.	Weight, kg		Time of Study after Bypass, Mo.	No. of Children
		Preoperative	Postoperative		
1	25	126	76	11	3
2	34	145	97	9	2
3	46	102	76	12	3
4	34	112	80	8	0
5	26	119	85	10	0
6	44	122	75	9	5
7	25	148	100	8	0
8*	30	131	109	3	4
			80	9	
Mean	33	125†	87†	8.8	2.1

* Patient was evaluated twice during the postoperative period.
† P value of difference between preoperative and postoperative values < 0.005.

Institutet, Sweden) was administered intravenously at a rate of 1 ml/minute. Duodenal bile-rich fluids were collected by aspiration. Three to five bile samples were collected on successive days before and approximately nine months after surgery. The 5 ml samples were immediately heated to 55° for ten minutes and then were stored at −20° until analysis. One patient (8) had two postoperative studies at three and nine months after the bypass.

Biliary Lipid Determinations

Prior to extraction, all samples were heated to 37° and agitated for one minute to disperse insoluble cholesterol. Extraction was then performed using the method of Flock et al.[5] The upper methanolic water phase was collected for bile salt determinations. Volumes were reduced to twice the bile sample volume with a Swissco vacuum evaporator at 40°. Bile salts were estimated by the method of Turnberg and Anthony-Mote.[20] The methanolic bile salt solutions were diluted from one-tenth to one one-hundredth with distilled water prior to assay. All determinations were performed with duplicate samples, using a Beckman DU-2 spectrophotometer. Reproducibility was greater than 95% and recovery of an internal standard was 98–103%. The organic phase was used for lecithin (phospholipid) and cholesterol determinations. The method of Rosenthal and Han was used to estimate phospholipid.[15] Cholesterol was estimated by the method of Abell et al.[1] Recovery with both these methods was between 95 and 100%.

Biliary lipid concentrations were used to evaluate the lithogenicity or cholesterol saturation of bile. The lithogenicity of each bile sample was assessed by the phase diagram triangular coordinates of Admirand and Small;[2] by the bile salt and phospholipid to cholesterol ratios as described by Isaksson et al.;[9] and by the cholesterol saturation index of Swell *et al.*[18] We also devised a lithogenicity score (LS) from the combined results with a minimum value of 0 and a maximum of 3. This was calculated as follows:

$$LS = \frac{L}{N}$$

where L = the total number of lithogenic measurements by three methods; N = the number of bile samples which were evaluated. The lithogenic score,

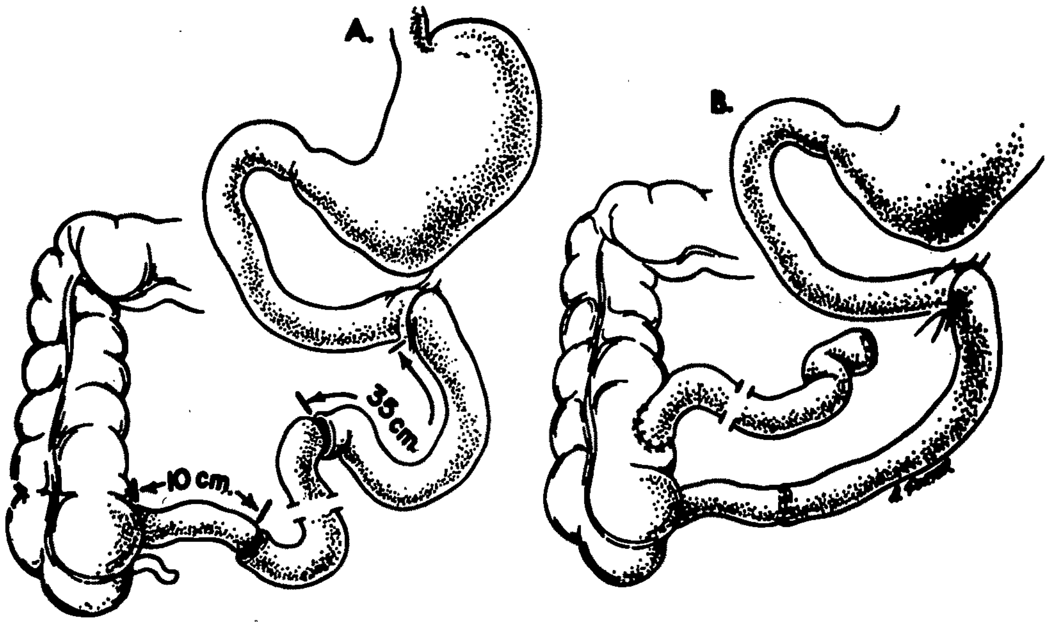


FIG. 1. Jejunoileal bypass as performed by us.

therefore, is an index of the cholesterol saturation of bile samples of three methods.

Glycine/Taurine Ratio

Bile salt conjugation with glycine and taurine was estimated from the concentrations of the conjugated bile salts after separation by thin-layer chromatography on silica gel G according to the method of Gregg.[8] All samples were heated and agitated at 37° for five minutes prior to application to thin layer chromatography plates (silica gel G, Quantum Industries, Fairfield, New Jersey). After centrifugation at 5000 × g, 25 μl samples were applied to each of four prescored channels on activated plates. Standards of glycocholate, glycochenodeoxycholate, glycodeoxycholate, glycolithocholate, taurocholate, taurochenodeoxycholate, cholate, and chenodeoxycholate were also applied to each plate. The plates were heated to 60° and were kept at that temperature for 15 minutes. After the plates cooled to room temperature, they were placed in a developing tank which had been allowed to equilibrate for one hour with a solvent system of iso-octane: isopropyl ether: glacial acetic acid: isopropyl alcohol: 2:1:1:1. When the solvent front was 1–2 cm from the top edge, the plates were removed, placed horizontally, and the solvents were allowed to evaporate. The dried plates were sprayed with a ten per cent phosphomolybdic acid-alcohol solution and heated at 100° for 20 minutes to visualize the bile salt standards. The appropriate areas and adjacent strips (controls) were removed. Glycine conjugated bile salts were separated, and taurine conjugates were pooled; the bile salts were dissolved into 2.5 ml 0.1M sodium pyrophosphate, pH 10.8. After centrifugation at 3000 × g, two aliquots were removed for bile quantification by the 3-α-hydroxysteroid dehydrogenase method of Turnberg and Anthony-Mote.[20] Bile salt concentration of each conjugate minus the control was the amount of glycine or taurine conjugate in bile. The relative proportion of glycine and taurine conjugation is expressed as the glycine/taurine ratio (G/T).

Statistical Methods

The Wilcoxon's matched-pair, ranked-sign test was used to evaluate differences between the pre- and postoperative groups.[16] The Mann-Whitney U-test was used for the evaluation of the effect of the bypass in the individual patients.[16]

Results

Following jejunoileal bypass for obesity, nine of the 101 patients developed biliary calculi during a mean follow-up period of 29.6 months. In eight of the 101 patients, the pre- and postbypass biliary concentrations of lecithin, cholesterol and bile salt have been evaluated. One patient (4) was excluded from the study; slight fibrosis of the hepatic parenchyma was evident in a liver biopsy specimen taken at the time of bypass and severe fibrosis was demonstrated eight months after the bypass. In none of the other seven patients was there any evidence of pre- or postoperative fibrosis. Following jejunoileal bypass, the overall effect on bile composition was a significant decrease in the biliary cholesterol ($p < 0.05$) and bile salt ($p < 0.05$) concentrations; the lecithin concentration, on the other hand, was not altered to a statistically significant degree (Table 2).

The per cent mean molar biliary composition

$$\frac{\text{moles of biliary lipid}}{\text{moles of total biliary lipids}} \times 100$$

for each patient was evaluated by three methods to establish a lithogenicity score for cholesterol satura-

TABLE 2. *Biliary Lipid Concentration (mM)**

Patient Number	Lecithin		Cholesterol		Bile Salt	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
1	0.36 ± 0.11	1.10 ± 0.86	1.66 ± 0.45	0.85 ± 0.06	15.87 ± 0.32	10.63 ± 1.06
2	0.64 ± 0.51	1.36 ± 0.55	2.14 ± 0.54	1.73 ± 0.30	11.42 ± 2.23	11.75 ± 3.53
3	10.15 ± 9.71	1.71 ± 0.90	13.18 ± 7.32	0.57 ± 0.19	56.80 ± 14.46	7.82 ± 2.58
4†	0.80 ± 0.80	0.10 ± 0.04	0.61 ± 0.33	0.07 ± 0.02	3.62 ± 2.15	13.25 ± 3.82
5	2.73 ± 2.74	3.69 ± 1.20	3.38 ± 0.41	2.00 ± 0.78	18.07 ± 0.36	12.14 ± 2.69
6	17.17 ± 11.75	14.10 ± 10.47	3.08 ± 1.86	4.45 ± 2.11	40.50 ± 33.92	36.87 ± 15.94
7	2.27 ± 1.92	1.95 ± 1.45	1.27 ± 0.10	1.66 ± 0.80	11.85 ± 3.30	9.50 ± 2.23
8	10.72 ± 14.18	3.78 ± 2.92	8.53 ± 4.17	2.49 ± 1.26	46.75 ± 31.68	17.60 ± 6.02
		4.58 ± 3.11		0.84 ± 0.89		16.62 ± 11.28
p-value‡	NS		<0.05		<0.05	

* Mean ± Standard Deviation.

† This patient was excluded from the study group because of post-bypass severe hepatic fibrosis and hepatic dysfunction.

‡ Significance of difference between pre- and post-bypass values determined by the Wilcoxon's matched-pair ranked-sign test.

NS = not significant at p = 0.05.

TABLE 3. *Biliary Cholesterol Saturation as Determined by Three Methods*

	Preoperative					Postoperative				
Patient	Number*	Isaksson[14]	Admirand[2]	Swell[29]	Lithogenicity Score	Number*	Isaksson[14]	Admirand[2]	Swell[29]	Lithogenicity Score
1	3	2	3	3	2.7	3	0	2	0	0.7
2	4	4	4	4	3.0	4	3	4	2	2.2
3	5	4	4	4	2.4	5	0	0	0	0
4†	5	5	5	4	2.8	4	0	0	2	0.5
5	4	4	2	4	2.5	5	4	1	3	1.6
6‡	5	0	0	0	0	4	2	1	1	1.0
7	4	0	2	0	0.5	4	4	3	2	2.2
8§	4	4	3	3	2.5	5	3	4	2	1.8
						4	0	0	0	0
Mean ± SEM	4.1 ± 0.3	2.6 ± 0.7	2.6 ± 0.5	2.6 ± 0.7	1.9 ± 0.4	4.2 ± 0.2	2.0 ± 0.6	1.9 ± 0.6	1.2 ± 0.4	1.2 ± 0.3

* The number of bile samples in the collection period.

† Patient excluded from study group because of hepatic fibrosis.

‡ Patient developed cholelithiasis.

§ Patient studied twice postoperatively.

tion, and the results are presented in Table 3. Of the eight patients, the overall lithogenicity decreased in six and increased in two; one of the later two patients (6) developed cholelithiasis by the time of the postoperative study. Another patient (8), who was studied twice during the postoperative period, had fewer cholesterol-saturated bile samples in the later study.

The alterations in the individual bile salts and the conjugation pattern of bile salts were also evaluated (Table 4). A significant ($p < 0.05$) decrease in the proportion of glycochenodeoxycholate occurred following jejunoileal bypass. No statistically significant, postoperative change was seen with glycocholate or glycodeoxycholate, although in six of seven patients the proportion of glycodeoxycholate increased following bypass. There was also a significant ($p < 0.05$) increase in the glycine/taurine (G/T) ratio after bypass; patient 7, who developed cholelithiasis following the bypass, had a postoperative G/T ratio of 11.5.

Discussion

The incidence of cholelithiasis following jejunoileal bypass has been evaluated in 101 patients. Since 31 (30.7%) of these patients developed biliary calculi prior to bypass surgery, only 70 (69.3%) patients were at risk to develop gallstones after bypass. Nine (12.9%) developed calculi during a mean follow-up period of 29.6 months. The incidence of postbypass cholelithiasis in this series, therefore, is 5.2% per year. The average age of our patients at the time of bypass was 33.7 years. Assuming that no patient developed biliary calculi before 20 years of age, the prebypass cholelithiasis in-

TABLE 4. *Proportion of Individual Bile Salts* and the Glycine/Taurine Conjugation Ratios†*

	Preoperative				Postoperative			
Patient	% GC	% GCDC	% GDC	G/T	% GC	% GCDC	% GDC	G/T
1	66	27	7	6.0	60	27	13	5.5
2	53	44	3	2.3	58	22	20	4.0
3	61	32	7	1.9	57	27	16	2.8
4§	54	46	0	5.0	33	67	0	11.6
5	45	27	28	7.1	66	24	10	9.0
6‖	57	34	9	6.2	60	30	10	11.5
7	53	39	8	5.6	59	34	7	5.2
8	59	39	2	3.4	65	35	0	5.1
					59	25	16	3.9
Mean ± SEM	56.3 ± 2.6	34.6 ± 2.4‡	9.1 ± 3.3	4.6 ± 0.8‡	60.5 ± 1.1	28.0 ± 1.6‡	11.5 ± 2.2	5.9 ± 1.0‡

* Expressed as $\frac{\text{moles of specific bile salt} \times 100}{\text{moles of total bile salts}}$

† Expressed as a molar ratio.

‡ p value of difference between the pre- and post-bypass values is <0.05.

§ Patient excluded from study because of hepatic fibrosis.

‖ Patient developed cholelithiasis.

GC = glycocholate.
GCDC = glycochenodeoxycholate.
GDC = glycodeoxycholate.
G/T = glycine/taurine ratio.

cidence was 30.7% in 13.7 years (33.7–20), or 2.2% per year. This suggests an increased incidence of cholelithiasis following jejunoileal bypass, and confirms previous reports.[3,13]

The etiology of cholesterol cholelithiasis may be due to infection, stasis, or due to change in bile composition. There is no evidence that jejunoileal bypass is associated with biliary infection or stasis; therefore, we studied the compositional changes of bile. The physicochemical properties of the components of bile seem to be related to the pathogenesis of cholelithiasis. Cholesterol is a lipid and is only slightly soluble in aqueous solutions. In bile, cholesterol solubility is enhanced by the detergent properties of bile salts and lecithin and the formation of mixed micelles.[2] Since the molar composition of these biliary molecules determines cholesterol solubility or saturation, bile composition was studied in eight morbidly obese patients prior and following bypass surgery.

Several investigators have suggested graphic or numerical techniques for determining the lithogenicity of bile. In 1954, Isaksson reported that the bile from more than 70% of patients with cholesterol cholelithiasis had a bile sale + lecithin/cholesterol ratio less than 11;[9] bile from 93% of male patients without gallstones had a ratio above 11. Admirand and Small[2] studied the interaction of biliary lipids *in vitro* by varying the concentrations of bile salts, lecithin and cholesterol. When they plotted their data on triangular coordinates, a micellar zone of cholesterol solubility was clearly demarcated. Above this line, cholesterol supersaturation occurred. A similar graphic approach has been suggested by Swell et al.[18] but in a rectilinear plot. The cholesterol saturation index as determined by this method is based on the bile salt/cholesterol to bile salt/lecithin ratio.[18] Both graphic approaches, however, vary with the percentage of solute in the bile sample. Since the indication of biliary lithogenicity varies somewhat with these methods, all bile samples were evaluated by the three previously described methods.

As seen in Table 3, some variation exists in the cholesterol saturation as determined by these three methods. We, therefore, devised a lithogenicity score from the combined results with a minimum value of zero and a maximum of three. The lithogenicity score decreased in six and increased in two patients. None of the former and one of the latter developed biliary calculi. The average preoperative lithogenicity score was 1.9 ± 0.4 which decreased postoperatively to 1.2 ± 0.3. Therefore, an alteration in the relative concentrations of biliary lipids did not seem to completely explain the increased incidence of cholelithiasis following jejunoileal bypass.

Our results indicate that jejunoileal bypass is associated with a decrease in biliary cholesterol and bile salt concentration while lecithin concentration is unchanged. After bypass there is a significant increase in fecal bile salt loss, which is followed by a compensatory increase in hepatic bile salt synthesis. In spite of this compensatory increase, however, eventually the bile salt pool size becomes reduced.[14,17] Since a diminished bile salt pool size often precedes cholesterol gallstone formation,[4] a casual relationship between a reduced pool size and gallstone formation may exist.

In vitro, the relative cholesterol dissolving power of bile salts, in decreasing order, is deoxycholate, chenodeoxycholate and cholate.[19] Studies on bile from gallbladders with gallstones, however, suggest that this may not be true. Our results suggest an overall increase in deoxycholate and a decrease in chenodeoxycholate following bypass. In the patient who developed biliary calculi following bypass, the chenodeoxycholate content has decreased without a significant change in the cholate content of bile.

Since the formation and stability of micellar suspensions in bile depends upon the relative strengths of the zeta potential of the biliary lipids and the Van der Wals forces, the presence of a highly negative polar group, which would increase the zeta potential, would prevent gallstone formation.[12] Taurine has a negative SO_3 group and would tend to protect against cholelithiasis; an increase in the glycine/taurine (G/T) ratio of conjugated bile salts, therefore, may promote gallstone formation. In this group of patients there was a significant overall increase in the G/T ratio following bypass. In the patient who developed gallstones, the G/T ratio has increased from a preoperative value of 6.2 to a postoperative ratio of 11.5. An alteration in the G/T ratio, therefore, may be the most significant factor in the etiology of gallstone formation following jejunoileal bypass.

References

1. Abell, L. L., Levy, B. B., Brodie, B. B. and Kendall, F. E.: A Simplified Method for the Estimation of Total Cholesterol in Serum and Demonstration of its Specificity. J. Biol. Chem. 195:356, 1952.
2. Admirand, W. H. and Small, D. M.: The Physicochemical Basis of Cholesterol Gallstone Formation in Man. J. Clin. Invest. 47:1043, 1968.
3. Baber, J. D., Jr., Hayden, W. F. and Thompson, B. W.: Intestinal Bypass Operations for Obesity. Am. J. Surg. 126:769, 1973.
4. Bell, C. C., Jr., Vlahcevic, Z. R., Prazick, J., et al.: Evidence that a Diminished Bile Acid Pool Precedes the Formation of Cholesterol Gallstones in Man. Surg. Gynecol. Obstet. 136:961, 1973.
5. Flock, J., Lees, M. and Sloane-Stanley, G. H.: A Simple Method for the Isolation and Purification of Total Lipids from Animal Tissues. J. Biol. Chem. 226:497, 1957.

6. Freeman, J. B., Meyer, P. D., Printen, K. J., et al.: Analysis of Gallbladder Bile in Morbid Obesity. Am. J. Surg. 129:163, 1975.
7. Friedman, G. D., Kannel, W. B. and Dawber, T. R.: The Epidemiology of Gallbladder Disease. J. Chronic Dis. 19:273, 1966.
8. Gregg, J. A.: New Solvent Systems for Thin-layer Chromatography of Bile Salts. J. Lipid Res. 7:579, 1966.
9. Isaksson, B.: On the Lipid Constituents of Bile from Human Gallbladder Containing Cholesterol Gallbladder Containing Cholesterol Gallstones. A Comparison with Normal Human Bladder Bile. Acta Soc. Med. Ups. 59:277, 1954.
10. Mabee, T. M., Meyer, P., DenBesten, L., et al.: The Mechanism of Increased Gallstone Formation in Obese Human Subjects. Surgery 79:460, 1976.
11. Nakayama, F. and van der Linden, W.: Bile from Gallbladder Harboring Gallstone: Can it Indicate Stone Formation? Acta Chir. Scand. 136:605, 1970.
12. Ostrowitz, A. and Gardner, B.: Studies of Bile as a Suspending Medium and Its Relationship to Gallstone Formation. Surgery 68:329, 1970.
13. Payne, J. H., DeWind, L., Schwab, E. E., et al.: Surgical Treatment of Morbid Obesity: Sixteen Years of Experience. Arch. Surg. 106:432, 1973.
14. Quaade, F., Juhl, E., Feldt-Rasmussen, K., et al.: Blind-loop Reflux in Relation to Weight Loss in Obese Patients Treated with Jejunoileal Anastomosis. Scand. J. Gastroenterol. 6:537, 1971.
15. Rosenthal, A. R. and Han, S. C.: Phosphorus Determination in Phosphoglycerides from Thin-layer Chromatograms. J. Lipid Res. 10:243, 1969.
16. Sokal, R. R. and Rohlf, F. J.: Biometry. San Francisco, W. H. Freeman and Company, 1969.
17. Stein, T. and Wise, L.: Bile Salt Metabolism Following Jejunoileal Bypass for Morbid Obesity. Ann. Surg. 185:67, 1977.
18. Swell, L., Bell, C. C., Jr., Gregory, D. H. and Vlahcevic, Z. R.: The Cholesterol Saturation Index of Human Bile. Dig. Dis. 19:261, 1974.
19. Tamesue, N., Inone, T. and Juniper, K., Jr.: Solubility of Cholesterol in Bile Salt-Lecithin Model Systems. Dig. Dis. 18:670. 1973.
20. Turnberg, L. A. and Anthony-Mote, A.: The Quantitative Determination of Bile Salts in Bile Using Thin-layer Chromatography and 3α-hydroxysteroid Dehydrogenase. Clin. Chim. Acta 24:252, 1969.

A Density Test for the Intraoperative Differentiation of Parathyroid Hyperplasia from Neoplasia

CHIU-AN WANG, M.D.,* SIDNEY V. RIEDER, PH.D.†

From the Departments of Surgery and Clinical Chemistry of the Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts

A simple, instant, and reliable test called the Density Test, based on the difference in density between the normal and the diseased parathyroid tissue, was performed intraoperatively in 73 patients with primary hyperparathyroidism. Whereas the normal parathyroid tissue floated, the diseased tissue invariably sank in a mannitol solution with a density range between 1.049 and 1.069. With the aid of this test, a diagnosis of adenoma was made in 66 patients and of primary hyperplasia in the remaining seven. In every case the diagnosis was subsequently confirmed. Forty-two of the 66 patients with an adenoma (64%) had a unilateral exploration of the neck. The Density Test saved these patients from an unnecessary contralateral exploration by the finding of an adenoma and a normal second gland in the same side of the neck. These data show that the Density Test is useful in the intraoperative diagnosis of a diseased from a normal parathyroid tissue. Tissue that sinks within the density range of 1.049 and 1.069 is without exception diseased and should therefore be either partially or completely excised even if the gland is of average size or only of slight enlargement. If it does not sink, it is virtually certain to be normal and should be spared. The Density Test provides a valuable clue in the differentiation of primary parathyroid hyperplasia from neoplasia.

EVER SINCE THE FIRST recognition of primary hyperplasia as a pathologic entity of hyperparathyroidism,[1,4] its differentiation from a normal or an adenomatous parathyroid gland at the time of surgical exploration has posed a difficult problem to both surgeon and pathologist. The diagnosis of hyperplasia or adenoma can seldom be made on the basis of a single enlarged gland, and another gland is invariably needed for comparison. If this second gland is normal, the third, fourth, and sometimes, even a fifth gland are likely to be free of the disease. In this case, the enlarged gland is virtually certain to be a neoplasm, either the common adenoma or one of the rare carcinomas.[3,9] The so-called "double adenomas," if they indeed exist, are extremely rare, and we have not encountered a single case since 1958.‡ In contrast, if the second gland is also enlarged, involvement of all the other glands is certain, and primary hyperplasia may be expected. If, however, the second gland is averaged in size or slightly enlarged, difficulty arises as to whether it is diseased or not.

We have recently developed an objective test called the Density Test for the intraoperative differentiation of a normal and a diseased gland. On the basis of the results of this test, we were invariably able to differentiate a diseased from a normal gland and, hence, to make the diagnosis of either neoplasia or hyperplasia at surgery.

Materials and Methods

A sliver of tissue between 2 and 3 mm in thickness was taken from the central portion of an enlarged gland and another sliver, with the periglandular fat completely removed, from a gland of average size or of only slight enlargement. The slivers were then placed in a test tube with about 2 ml of 25 per cent mannitol solution (Fig. 1).§ By gradually diluting the mannitol solution with approximately 0.5 ml of water, a density was soon reached at which one or both tissues began to sink to the bottom. If only one tissue sank in this solution, there was clearly a difference in density, indicating that only one gland was involved with the disease and that diagnosis was virtually cer-

---

* Associate Clinical Professor of Surgery, Harvard Medical School, Visiting Surgeon, Massachusetts General Hospital, Boston, Massachusetts.

† Chief, Clinical Chemistry Laboratories, Massachusetts General Hospital, Boston, Massachusetts.

Reprint requests: Chiu-an Wang, M.D., Massachusetts General Hospital, Boston, Massachusetts 02114.

Submitted for publication: March 28, 1977.

‡ Prior to 1958, glands from 13 of 217 patients with primary hyperparathyroidism were diagnosed as double adenomas. Of these, six proved subsequently to be primary hyperplasia and seven have not been conclusively substantiated.

§ Mannitol injection USP 25% (12.5 g in 50 ml), Manufacturer: "Invenex," Chagrin Falls, Ohio 44022.

0003-4932-78-0100-0063-0075 © J.B. Lippincott Company

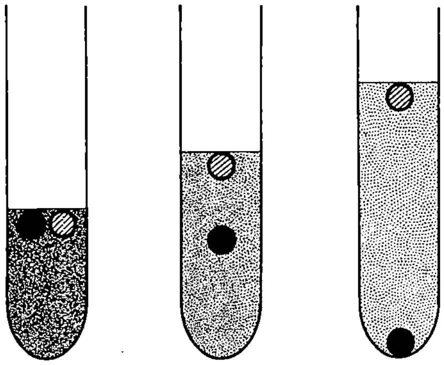


FIG. 1. Schematic Presentation of Density Test (See text). Cross-hatched circle = floats solid circle = sinks.

tain to be neoplasia, usually an adenoma. If both tissues sank, tissue from the remaining glands would likewise sink, the disease process was generalized, and the diagnosis was primary hyperplasia.

The density of the mannitol solution was determined by weighing 1 ml of the solution delivered into a tared weighing bottle from a calibrated 1 ml pipet. All measurements were made using a semimicroanalytic balance at room temperature of 23°. A slight change in temperature had no noticeable effect. The overall error in measurement was about ±0.002 gm/ml at the maximum. After the Density Test, the same tissues were studied by frozen section with fat stain and permanent histologic examination.

Clinical Data

The Density Test was performed intraoperatively in 73 patients with proven primary hyperparathyroidism. Nineteen of the patients were men and 54, women (Fig. 2). Sixty-one (82%) were between the ages of 40 and 69; the youngest patient was 14 and the oldest, 75.

In 52 patients, 2 ml of 25% mannitol solution diluted with about 0.5 ml of water as described above was used for the test (Table 1). In 46, the tissue from the enlarged gland sank readily in the solution and that from the gland of normal size floated; all 46 patients proved to have an adenoma. In the remaining six patients, the tissue from two or more glands sank almost simultaneously in the above solution, and all six patients were found to have primary hyperplasia.

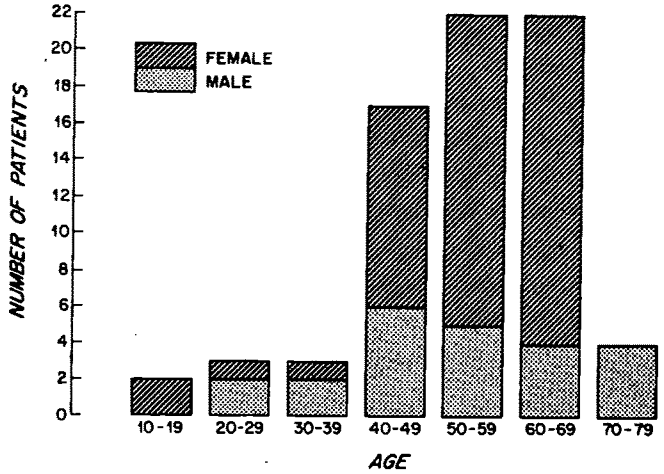


FIG. 2. Sex and Age Distribution of 72 Patients Who Underwent Density Test.

The density of the solution was determined in 28 cases (Fig. 3). It was found to be within a range of 1.049 to 1.069; the mean at which tissue from the enlarged gland sank was 1.055 ± 0.006 SD. In 12 others, tissue from the gland of normal size had remained afloat until the solution was further diluted with approximately 8 ml of water. Under these conditions, a new density was reached ranging from 1.010 to 1.038, with a mean of 1.017 ± 0.008 SD. These findings clearly indicate that there is a marked difference in density between the diseased and the normal parathyroid tissue.

For the remaining 21 patients, the density of the solution had been calibrated at 1.069 to 1.050 prior to the test (Table 2). This density was chosen as the lowest possible level at which a diseased parathyroid tissue would sink even when the degree of hyperparathyroidism was relatively mild. Twenty patients in this group had an adenoma and one had primary hyperplasia.

In the entire group of 73 patients, 66 had adenomas and seven, primary hyperplasia. Unilateral exploration was performed in 42 in whom an adenoma and a normal second gland were uncovered in the same side of the neck. Bilateral exploration was performed in 31 patients. Seven of these had primary hyperplasia; of the remaining 24, either the diseased gland was located in the side opposite that of the initial exploration or surgery was performed to verify the accuracy of the Density Test.

The diagnosis in each case was subsequently confirmed by the postoperative serum calcium determination, and in 44 patients, the plasma parathormone, preoperatively found to be elevated, returned to a normal range immediately after surgery.

Discussion

It is well known that stromal fat cells begin to appear in a normal parathyroid gland after puberty and continue to increase numerically until a person reaches 40. Thereafter, they diminish somewhat in number but never completely disappear even in later years.[2] Intracellular fat granules are generally abundant in a normal gland and are even more numerous in a normal gland suppressed by an adenoma.[8] In sharp contrast, there are few or no stromal fat cells or intracellular fat granules in a diseased parathyroid gland.* The Density

---

* With a mild degree of hyperparathyroidism, a few fat cells or fat granules may be present in a diseased gland. Their presence accounts for the relatively low density of some of these diseased tissues.

TABLE 1. *Clinical Data of Density Test Performed in 52 Patients with Primary Hyperparathyroidism*

Case No.	Gland(s)		Density of Solution	Diagnosis	Exploration of the Neck	Serum Calcium†		Plasma Parathormone‡	
	Floated*	Sank*				Preoperative	Postoperative	Preoperative	Postoperative
1	RU,LU LL	RL	1.050	Adenoma (RL)	Bilateral	11.8	8.6	12	2.5
2	RU	RL	1.055	Adenoma (RL)	Unilateral	11.6	8.6	38	3.5
3	LU RL,LL	RU	—	Adenoma (RU)	Bilateral	11.6	8.4	46	3.5
4	None	RL,LU	1.051	Hyperplasia	Bilateral	11.4	8.0	33	3.5
5	RU,LU LL	RL	—	Adenoma (RL)	Bilateral	10.6	8.4	20	5.0
6	LU LL	RU	—	Adenoma (RU)	Bilateral	12.8	8.0	41	4.5
7	LL	LU	1.055	Adenoma (LU)	Unilateral	12.2	7.8	27	5.0
8	RU	RL	—	Adenoma (RL)	Unilateral	11.7	9.2	23	2.5
9	RU	RL	1.051	Adenoma (RL)	Unilateral	11.7	8.8	20	5.0
10	RU	RL	—	Adenoma (RL)	Unilateral	11.0	8.8	26	5.0
11	None	LU,RU LL,RL	1.054	Hyperplasia	Bilateral	10.9	7.3	15	2.5
12	RL	RU	—	Adenoma (RU)	Unilateral	12.4	7.8	40	7.5
13	RU	RL	—	Adenoma (RL)	Unilateral	12.0	8.5	11	5.0
14	RL,LL	RU	—	Adenoma (RU)	Bilateral	12.0	8.4	21	5.0
15	RL	RU	—	Adenoma (RU)	Unilateral	13.0	9.3	45	3.0
16	None	RU,RL LU,LL	1.060	Hyperplasia	Bilateral	13.8	9.9	42	3.5
17	RL	RU	—	Adenoma (RU)	Unilateral	15.0	8.8	—	—
18	RL	RU	—	Adenoma (RU)	Unilateral	12.0	8.9	12	8.5
19	RL	LU	1.050	Adenoma (LU)	Bilateral	10.7	8.5	15	3.5
20	RL	LU	—	Adenoma (LU)	Bilateral	11.0	7.9	26	5.0
21	RL	RU	1.058	Adenoma (RU)	Unilateral	12.5	9.3	—	—
22	RL	RU	—	Adenoma (RU)	Unilateral	12.7	6.9	60	9.0
23	RL	RU	—	Adenoma (RU)	Unilateral	11.0	8.9	14	5.0
24	None	RU,LU RL,LL	1.058	Hyperplasia	Bilateral	12.0	8.0	11	4.0
25	RL	RU	—	Adenoma (RU)	Unilateral	11.4	9.3	13	5.0
26	RU RL,LL	LU	—	Adenoma (LU)	Bilateral	11.3	8.8	20	2.5
27	RU,RL LL	LU	—	Adenoma (LU)	Bilateral	12.0	8.0	—	—
28	RL	RU	—	Adenoma (RU)	Unilateral	12.6	8.8	20	3.0
29	None	RU,RL LU,LL	1.057	Hyperplasia	Bilateral	11.5	9.2	14	1.0
30	LL RU	LU	—	Adenoma (LU)	Bilateral	12.0	8.6	—	—
31	RL	LL	—	Adenoma (LL)	Bilateral	12.5	8.8	—	—
32	LU	LL	—	Adenoma (LL)	Unilateral	12.2	7.9	13.5	10
33	RU,LU	RL	—	Adenoma (RL)	Bilateral	11.6	8.7	—	—
34	RL	RU	1.064	Adenoma (RU)	Unilateral	11.0	9.0	14	5.0
35	None	RU,RL LU,LL	1.056	Hyperplasia	Bilateral	12.0	8.4	—	—
36	RU	RL	1.064	Adenoma (RL)	Unilateral	12.6	8.0	—	—
37	RU	RL	1.064	Adenoma (RL)	Unilateral	11.0	8.0	—	—
38	RU,RL LU	LL	1.062	Adenoma (LL)	Bilateral	12.0	8.0	—	—
39	RU,RL	LL	1.048	Adenoma (LL)	Bilateral	12.0	8.0	—	—
40	RU	RL	1.063	Adenoma (RL)	Unilateral	12.2	8.6	—	—
41	LL	RL	1.055	Adenoma (RL)	Bilateral	12.0	8.6	—	—
42	RL	RU	1.060	Adenoma (RU)	Unilateral	11.6	8.8	14	5.0
43	LU	LL	1.059	Adenoma (LL)	Unilateral	13.0	9.6	15	5.0
44	LU	RU	1.059	Adenoma (RU)	Bilateral	11.0	8.8	13	5.0
45	LU	LL	1.057	Adenoma (LL)	Unilateral	12.0	8.6	—	—
46	LL	LU	1.055	Adenoma (LU)	Unilateral	12.6	8.0	—	—
47	RU	RL	—	Adenoma (RL)	Unilateral	11.0	8.3	—	—
48	LL	LU	1.055	Adenoma (LU)	Unilateral	11.0	8.2	—	—
49	RU	LL	1.053	Adenoma (LL)	Bilateral	11.7	9.0	—	—
50	RL	RU	1.062	Adenoma (RU)	Unilateral	11.9	9.1	—	—
51	LU	LL	1.061	Adenoma (LL)	Unilateral	11.8	9.9	—	—
52	RU	RL	1.057	Adenoma (RL)	Unilateral	11.9	8.8	19	5.0

* In mannitol solution. (See text)

† Normal value = 8.4 to 10.4 mg/100 ml.

‡ Normal value = <10 microliter equivalent.

RU = Right upper gland.

RL = Right lower gland.

LU = Left upper gland.

LL = Left lower gland.

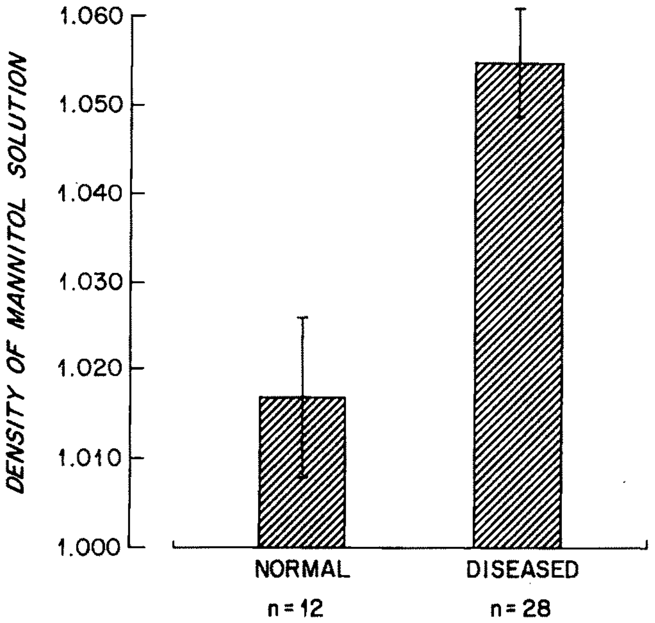


FIG. 3. Density Range in Which Parathyroid Tissue Sinks.

Test herein described is based on the marked difference between the fat content of the normal and that of the diseased parathyroid. With little or no fat, the diseased parathyroid tissue is heavier per unit volume than the normal tissue and would invariably sink in a solution with a density less than its own but still greater than that of the normal tissue. It is clear from this study that the Density Test can aid the surgeon in determining whether or not a parathyroid gland is diseased at the time of surgery.

It goes without saying that a surgeon must recognize the parathyroid gland when he sees one, although occasionally, he may confuse a fat lobule, a lymph node, or even a thyroid nodule with a parathyroid gland. However, a fat lobule may be recognized by its buoyancy in saline solution as opposed to parathyroid tissue which is heavier and will sink, and the firm-to-hard consistency of the lymph node and the thyroid distinguishes them from the parathyroid which is soft and malleable. Examination by frozen section can generally resolve uncertainty about the diagnosis.

In recent years, there has been disagreement over the surgical management of patients with primary hyperparathyroidism.[10] Some surgeons favor routine bilateral exploration of the neck[5,6] and excision of three and a half glands in every case.[7] Others advocate that surgery should always be performed on the basis of the pathologic entity of the disease.[3,9] Such disagreement stems from the difficulty in determining whether a gland

TABLE 2. *Clinical Data of Density Test Performed in 21 Patients with Primary Hyperparathyroidism*

Case No.	Gland(s) Floated*	Gland(s) Sank*	Density of Solution	Diagnosis	Exploration of the Neck	Serum Calcium† Preoperative	Serum Calcium† Postoperative	Plasma Parathormone‡ Preoperative	Plasma Parathormone‡ Postoperative
1	RL	LL	1.050	Adenoma (LL)	Bilateral	10.8	8.0	10	2.5
2	RL	RU	1.050	Adenoma (RU)	Unilateral	10.7	8.1	10.5	3
3	LL	LU	1.050	Adenoma (LU)	Unilateral	11.3	8.7	11	3
4	RL	RU	1.050	Adenoma (RU)	Unilateral	11.3	8.7	39	6
5	RL	RU	1.050	Adenoma (RU)	Unilateral	11.4	8.6	22	2.5
6	RU	RL	1.050	Adenoma (RL)	Unilateral	11.5	8.8	9.5	5.5
7	RL	RU	1.050	Adenoma (RU)	Unilateral	10.8	8.7	—	—
8	LL	RL	1.050	Adenoma (RL)	Bilateral	11.2	8.5	10	3
9	RL	RU	1.050	Adenoma (RU)	Unilateral	11.1	8.7	12.5	5
10	LU LL	RL	1.050	Adenoma (RL)	Bilateral	11.0	8.5	17	5
11	RU	RL	1.050	Adenoma (RL)	Unilateral	12.3	9.2	15	5.5
12	RL	RU	1.050	Adenoma (RU)	Unilateral	12.0	9.2	—	—
13	None	LU,LL RL	1.050	Hyperplasia	Bilateral	12.0	10.0	—	—
14	LL	LU	1.050	Adenoma (LU)	Unilateral	13.0	8.6	—	—
15	RU,LL LU	RL	1.049	Adenoma (RL)	Bilateral	10.4	8.6	—	—
16	LL	LU	1.049	Adenoma (LU)	Unilateral	12.3	8.9	—	—
17	RU RL	LU	1.049	Adenoma (LU)	Bilateral	12.0	8.8	—	—
18	RL	RU	1.049	Adenoma (RU)	Unilateral	10.8	8.6	10.5	3.5
19	RL	LU	1.049	Adenoma (LU)	Bilateral	11.1	8.2	—	—
20	RL	RU	1.049	Adenoma (RU)	Unilateral	12.0	9.0	44	5.5
21	RU RL	LU	1.049	Adenoma (LU)	Bilateral	11.0	9.5	—	—

* In mannitol solution. (See text)
† Normal value = 8.4 to 10.4 mg/100 ml.
‡ Normal value = <10 microliter equivalent.
RU = Right upper gland.
RL = Right lower gland.
LU = Left upper gland.
LL = Left lower gland.

of normal size or slight enlargement is diseased or not. We believe that this problem can generally be resolved with the aid of the Density Test and that there is seldom a need for routine bilateral exploration or radical resection of the glands unless the diagnosis clearly is primary hyperplasia. Forty—two (64%) of the 66 patients with the diagnosis of adenoma in this study were spared an unnecessary exploration of the opposite side of the neck because of an unequivocal diagnosis of an adenoma.

Critics may ask why another test is needed. It is true that a pathologic diagnosis can usually be obtained by frozen section examination and that an experienced pathologist can generally determine normality or disease in a gland by estimating the aggregate number of stromal fat cells and fat granules present in the tissue. We have found, however, that because fat cells and granules are not uniformly distributed, they may be scanty in one area and abundant in another. The diagnosis can be tenuous.* In the hands of a less experienced pathologist, diagnostic error may be expected even more frequently. With the Density Test, determination of the total fat content of the tissue eliminates the potential for error. Still another advantage of the Density Test is the ease with which it can be executed. It can confirm the diagnosis within two minutes as opposed to the 15 or 20 minutes required for an examination by frozen section.

Because the primary purpose of the Density Test is to demonstrate the difference in the density of the tissues under consideration, calibration of the exact density of the mannitol solution, although of academic interest, is not absolutely essential in each case. To have the mannitol solution readily available for the performance of the test, however, we have prepared one with a density of 1.049 to 1.050 and have found that at this level the diseased glandular tissue invariably sinks even if the degree of hyperparathyroidism involved is mild.

The accuracy of the Density Test is not affected by the size, weight, or volume of the parathyroid tissue. Nonetheless, a sliver of tissue should be no less than 2 mm in diameter. It should be free of periglandular fat, and if a rim of normal tissue is present in the diseased gland, it should be removed before the test.

Mannitol solution is found to be most satisfactory for the test because it neither alters nor damages the structure of the tissue. Thus, after the Density Test, the same sliver of tissue can be used for permanent histologic examination. Another point in its favor is that the mannitol solution is readily available in high concentration.

References

1. Albright, F., Bloomberg, E., Castleman, B., and Churchill, E. D.: Hyperparathyroidism Due to Diffuse Hyperplasia of All Parathyroid Glands Rather than an Adenoma of One. Clinical Study in Three Such Cases. Arch. Intern. Med. 54:315, 1934.
2. Castleman, B. and Mallory, T. B.: The Pathology of the Parathyroid Gland in Hyperparathyroidism. Am. J. Pathol. 11:1, 1935.
3. Cope, O.: The Story of Hyperparathyroidism at the Massachusetts General Hospital. N. Engl. J. Med. 274:1174, 1966.
4. Cope, O. Keynes, W. M., Roth, S. I. and Castelman, B.: Primary Chief-cell Hyperplasia of Parathyroid Glands. A New Entity in the Surgery of Hyperparathyroidism. Ann. Surg. 148:375, 1958.
5. Esselstyn, C. B., Jr., Levin, H. S., Eversman, J. J., et al.: Reappraisal of Parathyroid Pathology in Hyperparathyroidism. Surg. Clin. North Am. 54:443, 1974.
6. Haff, R. C. and Ballinger, W. F.: Causes of Recurrent Hyperparathyroidism After Parathyroidectomy for Primary Hyperparathyroidism. Ann. Surg. 173:884, 1971.
7. Paloyan, E., Lawrence, A. M., Baker, W. H. and Straus, F. H.: Near-total Parathyroidectomy. Surg. Clin. North Am. 49:43, 1969.
8. Roth, S. I. and Gallagher, M. J.: The Rapid Identification of "Normal" Parathyroid Glands by the Presence of Intracellular Fat. Am. J. Pathol. 84:521, 1976.
9. Wang, C. A.: Surgery of the Parathyroid Glands, *In* Welch, C. E., and Hardy, J. D. (eds), Advances in Surgery, Chicago, Year Book Medical Publishers, Inc., vol. 5, 1971, pp. 109–127.
10. Wang, C. A., Potts, J. T., Jr. and Neer, R. M.: Controversy of Parathyroid Surgery. Excerpta Medica International Congress Series No. 346:82, 1974.

---

* In seven instances in this study, a normal gland was interpreted as abnormal by the pathologist contrary to the findings of normality by the Density Test. Each gland was subsequently confirmed to be normal.

Does Adrenergic Activity Suppress Insulin Secretion During Surgery?

A Clinical Experiment with Halothane Anesthesia.

MARKKU ÄÄRIMAA, M.D., ERKKA SYVÄLAHTI, M.D., JARI OVASKA, M.B.

Peroperative inhibition of insulin release is widely attributed to increased alpha-adrenergic activity. To test this hypothesis serum insulin and glucose concentrations were measured at short intervals in 11 patients who underwent major surgery. Five patients were anesthetized with halothane and six with general anesthesia without halothane. The results were similar in both patient groups; halothane had no effect on insulin. This suggests that suppression of insulin under operations is probably not due to activation of the alpha-adrenergic receptors of the pancreatic beta-cells. The authors propose that suppression of insulin secretion during surgery may be caused by adrenaline, which, in competing for the glucose receptors, insensitizes the pancreatic beta-cells.

From the Departments of Surgery and Pharmacology the University of Turku, Turku, Finland

OPERATIVE TRAUMA CAUSES hyperglycemia without increased insulin secretion. This suppression of insulin secretion has been widely attributed to increased sympathetic activity.[1,2,13,22,24] Porte reported inhibition of insulin secretion during epinephrine infusion. It has been shown that alpha-adrenergic stimulation[21] and beta-adrenergic blockade[3] decrease glucose-stimulated insulin responses, which are increased by alpha-adrenergic blockade and beta-adrenergic stimulation.[22] Halothane is known to inhibit the alpha-adrenergic nervous system,[17] and after an initial inhibition, it stimulates the beta-adrenergic receptors.[23] It can, therefore, be assumed that if the peroperative suppression of insulin secretion is caused by sympathetic nervous activity, it could be counteracted by halothane anesthesia.

To investigate the effect of halothane on insulin secretion a clinical trial was planned. Patients undergoing major surgery (oesophageal resection) were selected for the study. General anesthesia with and without halothane was used. With the exception of halothane all the anesthetics used are known to be without sympatholytic properties. The effects of surgery and the different anesthetics on blood glucose (BG), serum immunoreactive insulin (IRI), and excreted catecholamines were studied. It was anticipated that in patients anesthetized with halothane there would be release of insulin suppression.

Patients and Methods

Eleven patients hospitalized for resection of oesophageal tumor were studied. The history of earlier disease was negligible except in the case of one patient who was suffering from sarcoidosis. Data concerning sex, age, weight, height, and time of operation are given in

---

Reprint requests: Markku Äärimaa, M.D., Department of Surgery, University Central Hospital of Turku, SF-20520 Turku 52, Finland.

Submitted for publication: March 30, 1977.

0003-4932-78-0100-0068-0075 © J.B. Lippincott Company

Table 1. Five of the patients were anesthetized with halothane (group I), whereas the others received general anesthesia without halothane (group II). Patients were selected at random for inclusion in the two groups. All the patients were informed of the study, and gave their consent.

Medication and Anesthesia

Each patient received intramuscularly 0.25 mg digoxine, 0.5 mg atropine and 50 mg pethidine half an hour before the operation. Anesthesia was induced with 200–250 mg thiomebumal (Intraval®) and 50–100 mg suxamethonium (Sukolin®). In group I the anesthesia was maintained with halothane, nitrous oxide–oxygen and muscle relaxant (pancurone-bromide, Pavulon®), in group II with combined nitrous oxide–oxygen, fentanyl (Fentanyl®) and pancuronebromide. Glucose was infused with a constant flow pump at a rate of 150 g/24 hours. The infusion was started at 8 a.m. on the day of operation, after a fast of eight hours.

Operation

The operation was begun with a laparotomy, to exclude abdominal metastases. This was followed by right-side thoracotomy and in each case the tumor was radically resected. The stomach was then liberally mobilized and pulled above the diaphragm in order to perform an esophagogastrostomy. There were no complications during surgery.

TABLE 1. *List of Patients and Operation Times*

	patients				operation		
	sex	age years	height cm	weight kg	commenced	duration	blood transfusions (units)
Group I							
1	F	55	164	73.0	9.30	3.55	2
2	M	68	170	83.0	9.15	4.10	3
3	M	41	162	57.5	9.30	3.30	1
4	F	66	155	71.0	9.25	3.50	0
5	F	74	153	67.0	9.45	3.15	0
Mean		61	161	70.0	9.30	3.45	1.2
Group II							
6	F	69	149	41.0	10.45	5.25	3
7	M	68	160	75.0	9.25	5.25	3
8	M	55	164	60.5	8.25	4.45	6
9	M	64	170	66.0	9.40	5.55	3
10*	F	52	158	50.0	9.15	4.35	4
11	M	67	184	78.0	9.30	3.30	3
Mean		63	164	62.0	9.30	4.45	3.7

* This patient had cortisone treatment for several years (prednisone, Me–Korti® 7.5 mg/d) for sarcoidosis. From the day of operation to the fifth postoperative day prednisone was replaced by hydrocortisone (Solu–Cortel® 200 mg/d) administered intramuscularly. The other patients had been healthy previously.

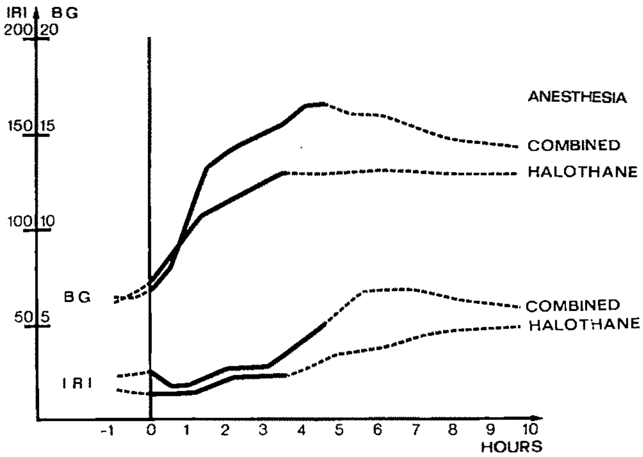


FIG. 1. Blood glucose and insulin concentrations. The zero point on the time axis indicates the beginning of the operation. Broken lines represent pre- and postoperative concentrations, continuous lines peroperative values. Insulin is given in uU/ml, blood glucose in mmol/l.

Samples and Laboratory Tests

Blood samples were taken at intervals of half an hour, starting at 8 a.m. on the day of operation. After noon the interval was extended to one hour, and after 14.00 (2 p.m.) to two hours. The results are given for the first ten hours. BG and IRI concentrations were measured. Determinations of the former were carried out by an autoanalyzer modification[10] of the method described by Hultman (1959); IRI was determined according to the method of Wide.[28] Twelve-hour urine samples were collected, beginning at 8 a.m. on the day of operation. Urinary adrenaline and noradrenaline were measured according to the method of Pekkarinen.[20]

Results

The mean values of serum insulin and blood glucose in both patient groups are presented in Figure 1. The zero point indicates the time of the skin incision. The mean curve was obtained by calculating the mean of the individual curves every half hour. It is possible that the concentrations indicated at the zero point are slightly too high because of the rising curves and the fact that no measurement was necessarily made at that time: this means that the angle of the slope may be too small during the first 30 minutes.

BG before premedication and anesthesia was 6.2 ± 1,2 mmol/l in group I and 6.3 ± 1,4 mmol/l in group II. The corresponding figures at the zero point were 7.1 ± 1,8 and 6.5 ± 1,1 mmol/l. The operations caused a rapid rise in the BG curve, 10.8 ± 2,7 mmol/l in group I

TABLE 2. *Excretion of Adrenaline (A) and Noradrenaline (NA) in ug/12 Hours*

GROUP I			GROUP II		
pat.	A	NA	pat.	A	NA
1	23.6	33.9	6	92.1	64.2
2	20.5	34.3	7	56.5	114.7
3	14.4	26.3	8	26.2	26.3
4	26.6	23.9	9	33.0	62.0
5	31.3	32.6	10	49.4	65.6
Mean	23.3	30.2	Mean	51.4	66.6
SD	6.4	4.8	SD	25.8	31.5

For one patient the urine sample was not obtained.

and 12.9 ± 3,4 mmol/l in group II being reached in 90 minutes. The elevation continued more gradually thereafter. After 3½ hours the concentrations were 12.9 ± 3,6 and 15.1 ± 1,7 mmol/l respectively. In group II the rise continued up to a value of 16.3 ± 2,9 mmol/l, which was reached at the end of the operation. The apparent difference in the concentrations between the two groups was not statistically significant.

IRI was 17.0 ± 1,7 uU/ml in group I and 21.5 ± 7,7 uU/ml in group II before premedication and anesthesia. The commencement of the operation did not cause any great change. One hour after the skin incision the concentrations were slightly reduced: 14.0 ± 6,5 and 15.5 ± 9.0 uU/ml in the respective groups. After this there seems to be a modest elevation: in group I the maximum peroperative value, 24.2 ± 17,1 uU/ml, was obtained after three hours of surgery. At this time the corresponding figure was 25.5 ± 12,3 uU/ml in group II, in which the rise continued up to a value of 46.5 ± 18,8 uU/ml at the end of the operation. In both patient groups the postoperative IRI concentrations were clearly higher than the pre- and peroperative values. There was no statistical difference between the two groups.

Excretetion of adrenaline and noradrenaline is shown in Table 2. In group I, 23.3 ug adrenaline and 30.2 ug noradrenaline was excreted in 12 hours and in group II the corresponding figures were 51.4 and 66.6 ug. The difference between the mean values of the two groups was not statistically significant.

Discussion

The results of the present study do not show any influence of halothane anesthesia on the peroperative suppression of insulin secretion. This finding does not support the theory that the suppression is due to increased alpha-adrenergic activity.

The action of catecholamines on insulin secretion has been studied by several authors. Porte[21] found that epinephrine inhibited insulin release in man. It has been shown that this inhibitory effect depends on the alpha-adrenergic receptors. The beta-adrenergic receptors are assumed to be similar or closely related to the glucose receptors[5] and beta-adrenergic stimulation increases insulin secretion. Porte and Robertson later showed that there is a sharp drop in insulin levels at the initiation of epinephrine infusion, with a nadir occurring within seven to ten minutes in normal subjects. They concluded that the early decrease, which is mediated by the alpha-adrenergic receptors, is followed by a recovery phase, during which the steady-state insulin levels are surpassed: also that the recovery phase is mediated by the beta receptors.[22]

The depressing action of halothane on the sympathoadrenal system is well documented.[17] Freiberg and his coworkers[6] measured catecholamine excretion in ten patients under halothane anesthesia. The excretion was significantly lower during anesthesia as compared with the initial values. Johnstone[12] confirmed the alpha-sympatholytic effect of halothane by volume-pulse digital pletysmography. An essential feature of this anesthetic is its direct action on the blood vessels and heart, but it has also been shown to cause depression of central sympathetic nervous activity in the cat.[25] Muldoon and his collaborators[16] performed experiments with isolated strips of saphenous vein from the dog. They concluded that the alpha-sympatholytic effect could be due to the inhibitory action of halothane on the release of noradrenaline from the nerve terminals.

The reaction of the beta-adrenergic system to halothane is different from the reaction of the alpha-adrenergic system. Price and his team[23] studied the effect of halothane on cardiac output and on the contractile force of the heart. After being suppressed initially, the beta receptors seem to be stimulated. Mäkeläinen and others[14] reported beta-stimulation in the rat: halothane induced FFA elevation, which could be obviated with beta-receptor blocking agents.

The effects of fentanyl and nitrous oxide, which were used for anesthesia in group II, differ from those of halothane. Fentanyl,[26] as well as nitrous oxide,[7] are reported to increase sympathetic nervous activity. Gött and Klench[9] measured two- to sixfold rises in plasma catecholamines during an operation under neurolept anesthesia in man. Nikki and his coworkers[19] were unable to prove constant elevation of plasma catecholamines in patients operated on under N_2O-O_2-anesthesia. They noted, however, that an increase in blood pressure and pulse rate was associated with elevation of plasma catecholamines during the operation. It therefore seems that in the case of group II the action of the anesthesia on the sympathetic nervous system was either neutral or stimulative and cannot be regarded as inhibitory.

In the present study, blood glucose levels and excretion of catecholamines were higher in group II than in group I. This may reflect a difference in the sympathetic activity in the two forms of anesthesia.

All patients in the present study responded to operative stress with a marked blood glucose elevation. Insulin secretion was also suppressed in all patients during the operation. The suppression was equally evident in both groups and halothane does not seem to have had any releasing effect on it. Eila and Esko Iisalo,[11] who compared the effects of halothane and combined anesthesias in children, have obtained similar results. They observed no differences in insulin responses, except that three hours after the beginning of the operations IRI was lower in the patients anesthetized with halothane. These observations fail to support the idea that alpha-adrenergic activity prevents insulin secretion during surgery. The sympathetic receptor functions that inhibit insulin secretion are alpha-adrenergic stimulation and beta-adrenergic inhibition. Halothane interferes with both of these functions.

Merin and his team[15] reported diminished insulin–glucose ratios under halothane anesthesia, without surgery. Halothane may thus affect the secretion of insulin directly. The suppression of insulin release involved seems, however, to be less than that caused by an operation. It has also been observed that halothane causes reversible inhibition of glucose-stimulated insulin secretion in isolated pieces from the pancreas of the rat.[8]

The possibility of catecholamine-induced inhibition of insulin secretion has also been tested with specific receptor-blocking drugs. It has not been possible to prove that alpha-adrenergic antagonists are effective in preventing insulin suppression either in man during operation[2] or in animals subjected to trauma.[18,27] In contrast to this, earlier adrenalectomy seems to prevent suppression in traumatized rats.[27] This finding shows that adrenomedullary catecholamines are involved in trauma induced insulin suppression.[27] It has also been shown, however, that adrenaline stimulates the pancreatic beta-receptors and increases insulin secretion. Porte and Robertson,[22] who demonstrated this, were of the opinion that alpha-adrenergic activity was responsible for the suppression.

The widely acccepted hypothesis that alpha-adrenergic activity is the cause of insulin suppression in surgery is not supported by the results of our investigation. Another possibility, we suggest, is that the glucose receptors, which are reported to be similar or closely related to the beta-adrenergic receptors, are blocked with excessive adrenaline. Insensitivity of the pancreas to glucose would be the consequence. As halothane has been shown to stimulate the same receptors, competition may perhaps explain the insulin inhibiting effect of this agent too.

It follows from the suggestion above that it ought to be possible to demonstrate an adrenaline concentration capable of insensitizing the pancreas, but not high enough to stimulate insulin secretion itself. Cerasi and his collaborators[4] made experiments with adrenaline infusions. They reported exquisite sensitivity of the pancreatic beta-cells to adrenaline, very small doses inducing inhibition. Their results show that the actions of adrenaline and glucose on insulin secretion are competitive.

As has been noted, alpha-adrenergic stimulation has also been reported to cause inhibition of insulin secretion. The purpose of this inhibitory dualism remains to be explained. The relative lack of insulin allows a rapid rise in BG and FFA, and, by preventing these substrates from escaping into the intracellular space, probably causes a persistent elevation of extracellular osmolality. An expansion of the vascular volume will ensue. Although this action may be mediated by beta-adrenergic activity during elective surgery, the alpha-adrenergic, predominantly neural, insulin inhibiting mechanism can be of importance in the state of shock.

References

1. Allison, S. P., Hinton, P. and Chamberlain, M. J.: Intravenous Glucose Tolerance, Insulin and Free-fatty-acid Levels in Burned Patients. Lancet 2:1113, 1968.
2. Allison, S. P., Tomlin, P. J. and Chamberlain, M. J.: Some Effects of Anesthesia and Surgery on Carbohydrate and Fat Metabolism. Br. J. Anaesth. 41:588, 1969.
3. Cerasi, E., Efendic, S. and Luft, R.: Role of Adrenergic Receptors in Glucose Induced Insulin Secretion in Man. Lancet 2:30., 1969.
4. Cerasi, E., Luft, R. and Efendic, S.: Antagonism Between Glucose and Epinephrine Regarding Insulin Secretion. A Dose-response Study in Man. Acta Med. Scand. 190:411, 1971.
5. Efendic, S., Cerasi, E. and Luft, R.: Arginine-induced Insulin Release in Relation to the Cyclic-AMP System in Man. J. Clin. Endocrinol. 34:67, 1972.
6. Freiberger, K. U., Hack, G. and Havers, L.: Verhalten der Harnkatecholamine bei der Kombinationsnarkose mit Halothan–Thalamonal. Anaesthesist 24:465, 1975.
7. Fukunaga, A. J. and Epstein, R. M.: Excitation During Nitrous-oxide-halothane Anesthesia in the Cat. Anesthesiology 39:23, 1973.
8. Gingerich, R., Wright, P. H. and Paradise, R. R.: Inhibition by Halothane of Glucose-stimulated Insulin Secretion in Isolated Pieces of Rat pancreas. Anesthesiology 40:449, 1974.
9. Gött, U. and Klensch, H.: Plasmakatecholaminänderungen bei verschiedenen Anästhesietechniken. *In*: Neue kliniinische Aspekte der Neuroleptanalgesie. Ed. W. F. Henschel. F. K. Schattauer Verlag, Stuttgart, New York 1970, p. 51.
10. Hyvärinen, A. and Nikkilä, E. A.: Specific Determination of Blood Glucose with O-toluidine. Clin. Chim. Acta 7:140, 1962.
11. Iisalo, E. V. M. and Iisalo, E. I.: personal communication.
12. Johnstone, M.: Digital Vasodilatation: A Sign of Anaesthesia. Br. J. Anaesth. 46:414, 1974.
13. Jordan, G. L. Jr., Fischer, E. P. and Lefrak, E. A.: Glucose

Metabolism in Traumatic Shock in the Human. Ann. Surg. 175:685, 1972.

14. Mäkeläinen, A., Nikki, P. and Vapaatalo, H.: Halothane-induced Lipolysis in Rats. Acta Anaesth. Scand. 17:170, 1973.
15. Merin, R. G., Samuelsson, P. N. and Schalch, D. S.: Major Inhalation Anesthetics and Carbohydrate Metabolism. Anesthesia and Analgesia. Curr. Res. 50:625, 1971.
16. Muldoon, S. M., Vanhouette, P. M., Lorenz, R. R. and Van Dyke, R. A.: Venomotor Changes by Halothane Acting on the Sympathetic Nerves. Anesthesiology 43:41, 1975.
17. Ngai, S. H.: Plasma Catecholamines–their Significance in Anesthesia. Anesthesiology 41:429, 1974.
18. Nijjar, M. S. and Perry, W. F.: Effect of Trauma on Serum Insulin Levels in Rabbits. Diabetologia 7:357, 1971.
19. Nikki, P., Takki, S., Tammisto, T. and Jäättelä, A.: Effect of Operative Stress on Plasma Catecholamine Levels. Ann. Clin. Res. 4:146, 1972.
20. Pekkarinen, A.: Fluorimetric determination of adrenaline and noradrenaline in urine. *In* Manninen, K.: Regulation of Increased Adrenomedullary Secretion by Drugs. Academic Dissertation, Turku, 1969, p. 26.
21. Porte, D.: A Receptor Mechanism for the Inhibition of Insulin Release by Epinephrine in Man. J. Clin. Invest. 46:86, 1967.
22. Porte, D. and Robertson, R. P.: Control of Insulin Secretion by Catecholamines, Stress, and the Sympathetic Nervous System. Fed. Proc. 32:1792, 1973.
23. Price, H. L., Skovsted, P., Pauca, A. L. and Cooperman, L. H.: Evidence for Beta-receptor Activation Produced by Halothane in Normal Man. Anesthesiology 32:389, 1970.
24. Ross, H., Johnston, I. D. A., Welborn, T. A. and Wright, A. D.: Effect of Abdominal Operation on Glucose Tolerance and Serum Levels of Insulin, Growth Hormone, and Hydrocortisone. Lancet 2:563, 1966.
25. Tauberger, G., Schulte am Esch, J. and Clostermann, M.: Wirkungen von Halothan auf den Kreislauf und den zentralen Sympathicustonus der Katze in Stickoxydul-Narkose. Anaesthesist 23:464, 1974.
26. Tauberger, G., Schulte am Esch, J. and Steinringer, W.: Der Einfluss kombinierter Narkosen mit Halothan under Neuroleptanalgesie auf die praeganglionäre Sympathicusaktivität, das Atemzentrum und den Kreislauf. Anesthesist 24:491, 1975.
27. Vigaš, M., Németh, Š. and Jurčovičová, J.: The Mechanism of Trauma-induced Inhibition of Insulin Release. Horm. Metab. Res. 5:322, 1973.
28. Wide, L.: Radioimmunoassays Employing Immunosorbents. Acta Endocrinol. 63, suppl. 142:207, 1969.

Hemodynamic Effects of Prolonged Hyperoxia

JON F. MORAN, M.D.,* WALTER G. WOLFE, M.D.†

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina

Experimental studies have consistently demonstrated the development of perivascular edema in the dog lung following prolonged exposure to 95% oxygen. This pathological change has been thought to result from capillary injury, but a direct effect secondary to left ventricular dysfunction has not yet been excluded. To evaluate the latter possibility, ten trained, awake dogs were prepared with monitoring of right and left atrial, systemic and pulmonary artery pressures, cardiac output, and mixed venous and arterial blood gases. Animals were exposed to an $F_IO_2 > 0.95$ for 48–70 hours. Radioactive 8–10 μ microspheres (^{141}Ce, ^{51}Cr, ^{85}Sr, ^{46}Sc) were injected into the left atrium at zero, six, 24, and 48 hours. PaO_2 was 480 ± 10 mm Hg during exposure, and the pulmonary shunt fraction increased from 11.3% to 16.9% ($p < 0.0001$) during 70 hours. Left atrial pressure fell from 9 ± 2 mm Hg to 3 ± 3 mm Hg ($p < 0.0001$), but cardiac output was constant at 2.7 ± 0.1 l/min. Pulmonary arteriolar resistance increased from 183 ± 20 dynes-sec-CM^{-5} to 791 ± 30 at 70 hours ($p < 0.0001$). Histologic sections of the lungs demonstrated the characteristic perivascular edema. Of particular interest was the fact that myocardial perfusion was significantly increased to all three layers of the ventricular wall at 24 and 48 hours. These data indicate that perivascular edema developing after exposure to high concentrations of oxygen is secondary to pulmonary capillary endothelial damage with no evidence that myocardial dysfunction occurs during this period.

DURING THE PAST 20 YEARS, with the development of efficient ventilators capable of delivering high concentrations of inspired oxygen, oxygen toxicity has become an increasingly well recognized clinical entity. Exposure of patients or experimental animals to greater than 95% oxygen for prolonged periods rapidly leads to diminished pulmonary function and perivascular interstitial pulmonary edema.[1,3,7,9,19] The pathogenesis of oxygen toxicity and, in particular, the mechanisms of fluid accumulation within the oxygen-toxic lung have not been clearly delineated. Although ultrastructural studies have implicated direct damage to the pulmonary capillary endothelium with subsequent leakage of fluid into the interstitium during hyperoxic exposure,[6,8] other evidence has implicated left ventricular failure in the pathogenesis of interstitial pulmonary edema during hyperoxia.[12,20,21]

During the course of experimentally induced oxygen toxicity in mechanically ventilated and spontaneously breathing dogs, ventilatory dead space was increased following 24 and 36 hours hyperoxic exposure and decreased sharply after 48 hours.[18] In the same study, pulmonary capillary filtration rate initially decreased and rose sharply after 48 hours exposure. These results are consistent with an initial vasoconstriction of the pulmonary vasculature in response to hyperoxia with a late, preterminal pulmonary vasodilatation. However, direct measurement of pulmonary vascular resistance at frequent intervals throughout the development of oxygen toxicity has not been previously reported.

In order to assess the possible roles of left ventricular dysfunction, maldistribution of coronary blood flow, and pulmonary vasoreactivity in the pathogenesis of fluid accumulation within the lungs during prolonged hyperoxia, continuous monitoring of hemodynamic variables and serial measurement of regional coronary blood flow in spontaneously breathing dogs exposed to greater than 95% oxygen was undertaken.

Methods

Ten mongrel dogs (13–18 kg) underwent sterile left thoracotomy under sodium pentobarbital (5 mg/kg) anesthesia. Sixteen gauge polyvinyl chloride catheters were implanted into the right and left atria, and the pulmonary and left subclavian arteries (Fig. 1). A silastic conduit (I.D. = 3 mm) was inserted through the anterior wall of the right ventricular outflow tract just beneath the pulmonic valve and sewn in place. The conduit and the four monitoring catheters were filled with heparin and their capped ends buried subcutaneously. Each animal was allowed to recover for a period of 3–6 weeks.

During the recovery period, each animal was trained to stand and lie quietly while loosely tethered in an

---

* Research Fellow of the North Carolina and American Heart Associations.

† Supported by USPHS Grant R01 HL 15877.

Reprint requests: Walter G. Wolfe, M.D., P. O. Box 3507, Duke University Medical Center, Durham, North Carolina 27710.

Submitted for publication: April 6, 1977.

0003-4932-78-0100-0073-0075 © J.B. Lippincott Company

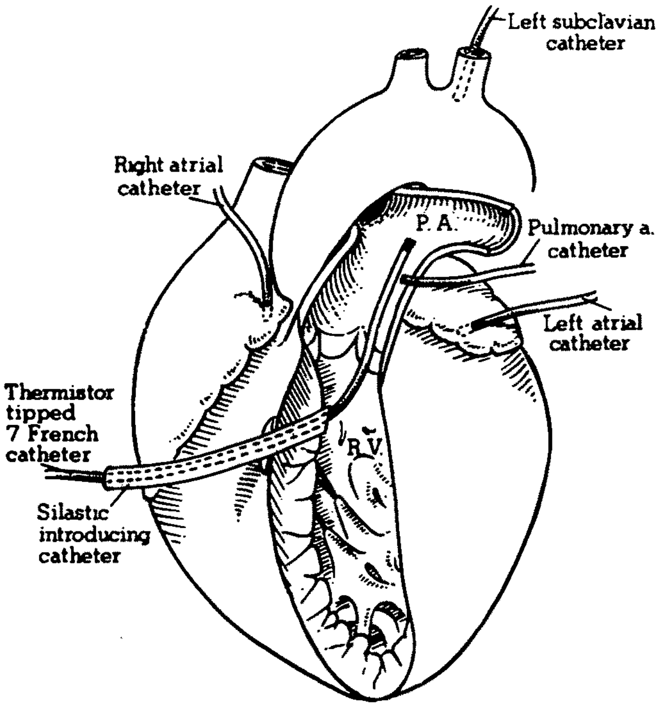


FIG. 1. Schematic drawing showing positioning of chronic hemodynamic monitoring catheters in the central circulation. Position of thermistor-tipped thermodilution catheter is shown after insertion through chronically implanted Silastic conduit.

environmental chamber (Fig. 2). The ends of the previously implanted catheters were exteriorized under local anesthesia following the completion of training. A thermistor-tipped 7F thermodilution cardiac output catheter was introduced through the Silastic conduit and the tip positioned in the main pulmonary artery under fluoroscopy. After a baseline chest x-ray was taken, each animal was loosely restrained within the environmental chamber and the four monitoring catheters connected to strain-gauge manometers through shielded fluid-filled 16 gauge connecting tubes for continuous monitoring of right and left atrial, pulmonary and systemic arterial pressure on an eight-channel recorder. Strain-guage manometers were rezeroed and calibrated against a mercury manometer every two hours. The thermistor-tipped pulmonary artery catheter was conncected to a thermodilution cardiac output computer. After baseline measurements were completed, the chamber was sealed and flushed with 100% oxygen.

All vascular pressures and core temperatures were recorded continuously. At two hour intervals arterial and mixed venous blood gases (P_{O_2}, P_{CO_2}, and pH) were analyzed by standard techniques, hemoglobin concentration was determined by the cyanmethemoglobin method, and cardiac output was measured in triplicate after the injection of a five per cent dextrose in water solution (4°) through the right atrial catheter. Oxygen tension within the chamber was maintained greater than 700 mm Hg and each animal remained in the chamber until death or 70 hours of exposure.

Prior to sealing the chamber and after six, 24, and 48 hours exposure to hyperoxia, radioactively labelled (^{141}Ce, ^{51}Cr, ^{85}ST ^{46}Sc) 7–10 μ microspheres were injected throught the left atrial catheter with reference sampling through the left subclavian artery catheter for later calculation of quantitative regional myocardial blood flow.[5] Animals surviving 70 hours exposure had chest x-rays prior to being sacrificed. At autopsy multiple lung sections were taken for histologic examination and the left ventricular free wall was carefully sectioned into subepcardial, midmyocardial, and sub-

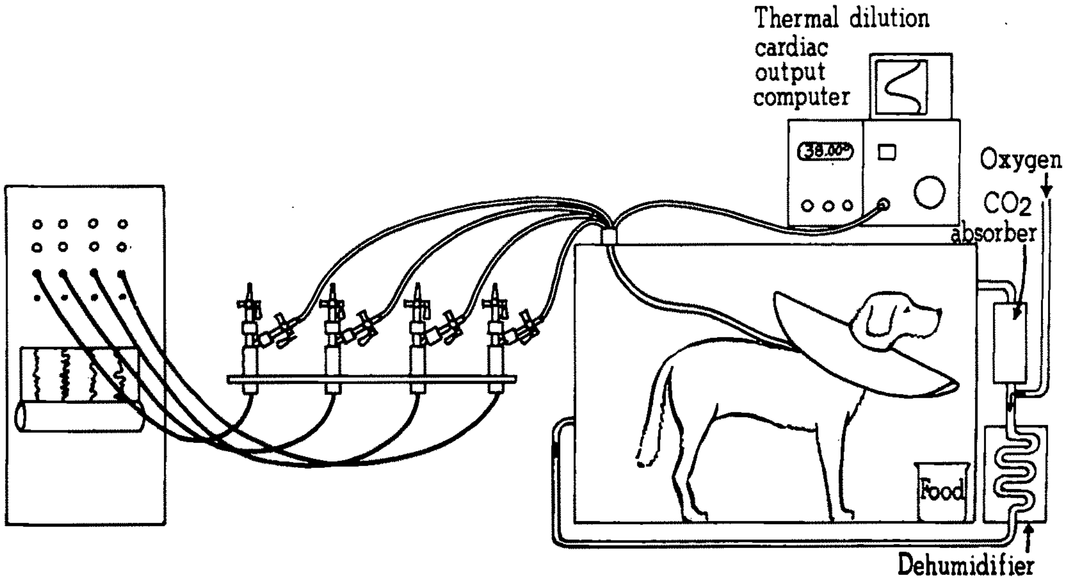


FIG. 2. Schematic diagram of the experimental preparation showing the dog within the sealed oxygen chamber with attached monitoring equipment.

endocardial layers for determination of regional myocardial perfusion.

Pulmonary shunt fraction (Q_SQ_T) was calculated from arterial and mixed venous blood gas values and hemoglobin concentration using a Severinghaus slide rule and the standard shunt formula. Systemic (SVR) and pulmonary (PVR) vascular resistances were calculated from the vascular pressures and the measured cardiac output (C.O.) using standard formulae. Blood gas and hemodynamic variables were correlated with length of exposure time to hyperoxia using a multiple linear regression computer program. The significance of changes in mean and regional myocardial blood flows during exposure was assessed using an analysis of variance computer program.

Results

All animals remained quiet in the chamber without agitation throughout the exposure period. After 40–48 hours of hyperoxic exposure, the breathing pattern gradually changed to slower and deeper inspiration. The respiratory rate fell to less than 10/min during the preterminal two or three hours. Mean survival for the ten animals was 57 hours, with survival times ranging from 46 hours to 70 hours. Only two dogs survived the entire 70 hour period.

All pre-exposure chest x-rays were normal except for minor postoperative blunting of the left costophrenic angle. Postmortem and postexposure chest x-rays showed a uniform ground-glass interstitial edema pattern throughout both lung fields. Histologic sections from all lobes of each animal showed the hallmarks of oxygen toxicity with perivascular cuffing, increased cellularity of alveolar septa, swelling of alveolar septa, and fluid accumulation within alveoli.

Core temperatures of all animals remained relatively normal (<39°) and arterial pH, arterial carbon dioxide tension (Paco_2), and heart rate were remarkably constant throughout the exposure period as indicated by the mean values ±2 standard errors for each of these parameters: pH = 7.44 ± 0.01; Paco_2 = 26.7 ± 0.5 mm Hg; and heart rate = 96 ± 5 beats/min.

Arterial oxygen tension (Paco_2) decreased very little with increasing time of exposure to hyperoxia (Fig. 3). However, Paco_2 fell precipitously in five animals just prior to their death, and a similar fall occurring within a two hour period may have been missed in several other animals. Overall, there was a relatively poor correlation ($r = 0.25$) between Paco_2 and hyperoxic exposure time. The animals were able to maintain nearly normal oxygenation until just prior to death when severe relative hypoxemia developed quite rapidly. Correspondingly, Q_S/Q_T rose relatively slowly with increasing exposure time (Fig. 3). However, the increase in Q_S/Q_T from 11.3% initially to 16.9% after 70 hours of exposure was highly significant ($p < 0.0001$).

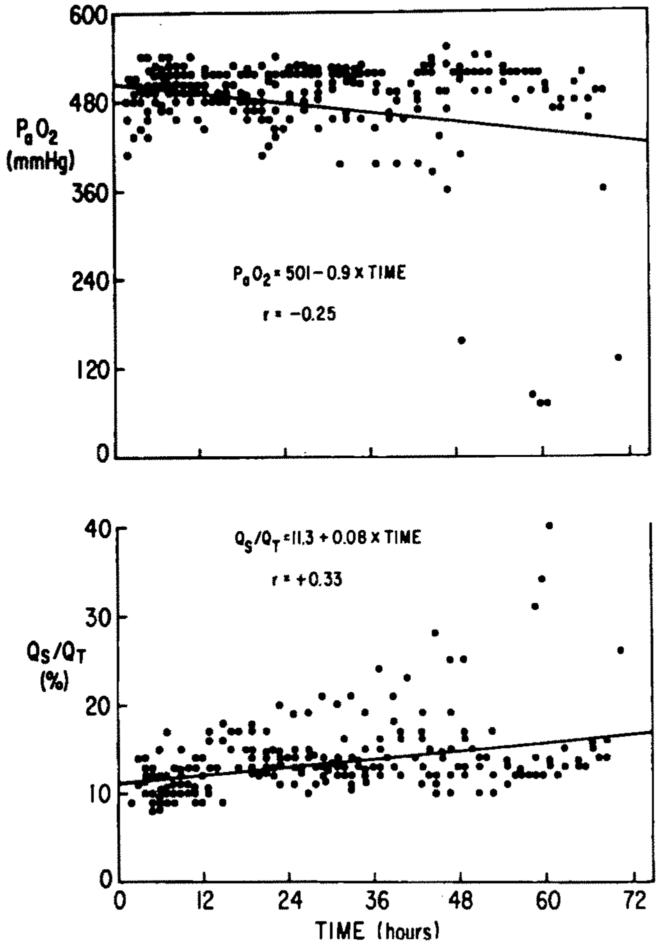


FIG. 3. Arterial oxygen tension (Pao_2) values and pulmonary shunt fraction (Q_S/Q_T) determinations plotted against time of exposure to hyperoxia ($F_IO_2 > 0.95$). The equation for each least squares linear regression line and the correlation coefficient (r) are given.

Central venous pressure and left atrial pressure decreased gradually during the exposure period while C.O. remained nearly constant over the 70 hour period (Fig. 4). The correlations between exposure time and the decreasing atrial pressures were not close ones, and there was practically no correlation between C.O. and exposure time ($r = -0.20$). Each animal was able to maintain a normal cardiac output with stable or slightly decreased left atrial and central venous pressures.

Both SVR and PVR rose significantly under the stimulus of prolonged hyperoxia (Fig. 5). However, the increase in SVR from hour 0 to hour 70 was less than 100%, and the correlation between rising SVR and the length of hyperoxic exposure was only moderately good ($r = 0.50$). The progressive increase in PVR during hyperoxia is initially very gradual but becomes very steep from 24 hours of exposure onward. The correlation between rising PVR and the square of the duration

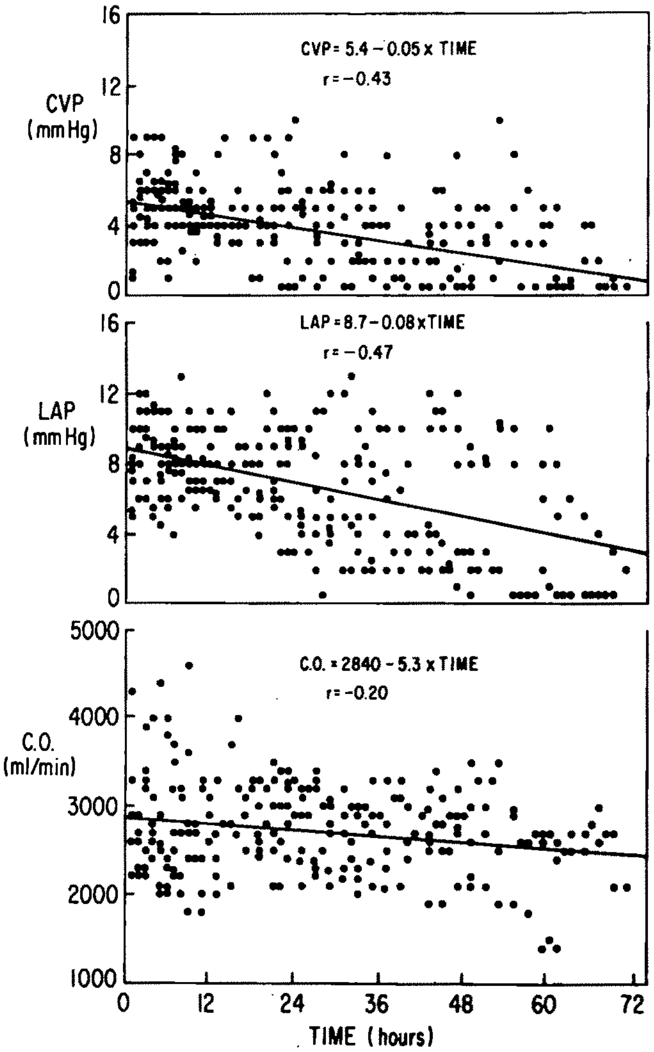


FIG. 4. Central venous pressures (CVP), left atrial pressures (LAP), and cardiac outputs (C.O.) plotted against time of exposure to hyperoxia ($F_IO_2 > 0.95$). The equation for each least squares regression line and the correlation coefficient (r) are given.

of hyperoxic exposure is excellent ($r = 0.82$). The equation

$$\mathrm{PVR}(\text{dynes-sec-cm}^{-5}) = 183 + 0.124\mathrm{X}(\mathrm{TIME\ (hrs)})^2$$

accurately describes the dependence of PVR on exposure time in these experiments. The PVR after 70 hours exposure extrapolated from this equation is 791 dynes-sec-cm^{-5}, a 430% increase from the initial levels. PVR correlated much better with exposure time than did any other of the measured variables.

Exposure to hyperoxia led to a uniform increase in left ventricular perfusion after 24 and 48 hours (Fig. 6). There was no change in blood flow to any layer of the left ventricle following six hours of hyperoxia, but perfusion was significantly increased to all three layers of the left ventricle after 24 ($p < 0.01$) and 48 ($p < 0.05$) hours of hyperoxia. The increases in flow to the subepicardial, midmyocardial, and subendocardial layers at 24 hours compared to control were 60%, 53% and 37% respectively. After 48 hours of hyperoxia, the increases in flow to the three layers compared to control were 33, 29 and 26% respectively. These increases occurred despite a constant or slightly decreased cardiac output.

Discussion

Prolonged exposure of man to pure oxygen causes a decrease in vital capacity, a decreased diffusing capacity, an increased Q_S/Q_T, increased ventilatory dead space, and a decreased Pa_{CO_2}.[1,3] However, breathing of 100% oxygen by patients for six to 24 hours caused no changes in Pa_{CO_2}, Q_S/Q_T, C.O., PVR, ventilatory dead space or compliance.[13,14] In the critically ill patients requiring high concentration oxygen therapy, there is no parameter that can be monitored in order to herald the onset of early oxygen toxicity.

Attempts to clarify the mechanism of pulmonary fluid retention during the early phases of oxygen toxicity

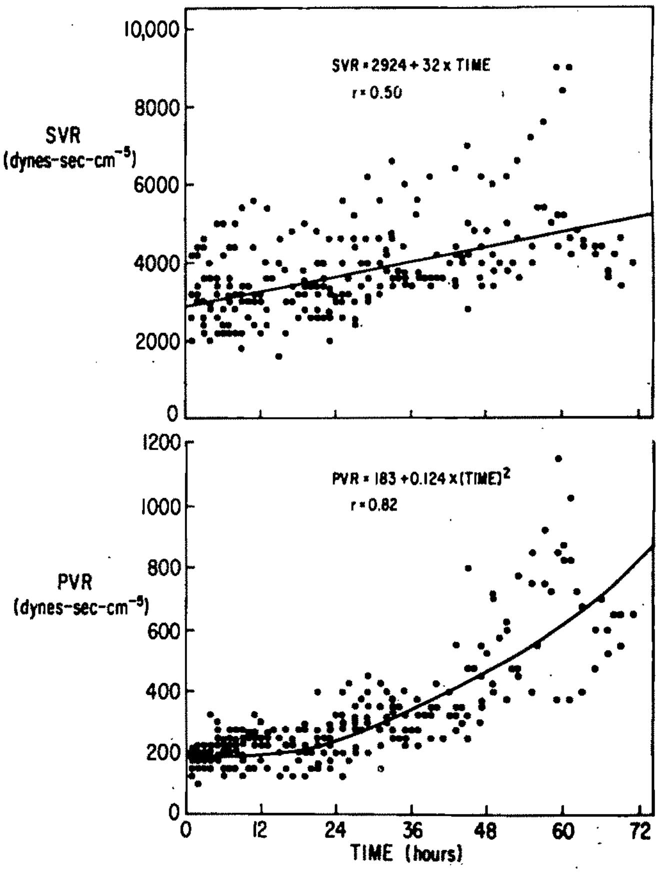


FIG. 5. Calculated systemic (SVR) and pulmonary (PVR) vascular resistances are plotted versus hyperoxic exposure time. The least squares regression lines relating SVR to exposure time and PVR to the square of exposure time are given with their respective correlation coefficients (r).

have been inconclusive in the past.[17] A variety of animal studies have yielded conflicting data implicating pulmonary vascular dilatation,[18] pulmonary vascular constriction.[4,16] and left ventricular failure secondary to acute systemic hypertension[20,21] or impaired myocardial blood supply[11,12] as the mechanism underlying early fluid retention in the oxygen-toxic lung. Each of these previous studies, however, was performed at hyperbaria, in anesthetized animals, or in excised heart–lung preparations. The cardiovascular responses of anesthetized animals can be quite different from the responses of conscious, unstressed animals.[15]

This study confirms the fall in Paco$_2$ after 48 hours of hyperoxia noted previously in dogs.[19] The increased frequency of blood gas sampling in this study revealed a long pleateau followed by a sudden precipitous decline in Paco$_2$ at between 48 and 70 hours, rather than a gradual, progressive decline. This abrupt fall in Paco$_2$ cannot be explained on the basis of progressive absorption atelectasis. Similarly, the rise in Q_S/Q_T was accelerated after 48 hours of hyperoxia.

Prolonged hyperoxia in conscious animals leads to increased PVR secondary to either pulmonary vasoconstriction or vascular obstruction. The elevation of PVR is not a reflection of elevated left atrial pressure, as left atrial pressure fell during hyperoxic exposure. As previously shown in man,[2,14] there was very little increase in PVR during the initial 24 hours of hyperoxia in these dogs and it is therefore unlikely that the eventually elevated PVR is caused by reflex vasoconstriction. Rather, direct oxygen damage to the pulmonary capillary endothelium leading to perivascular and interstitial edema[6,7] most likely causes progressive pulmonary capillary obstruction. Such a mechanism would explain the exponential rise in PVR after 24 hours exposure, if that were the critical length of exposure necessary for breakdown of pulmonary endothelial integrity. Once capillary leakage begins, PVR rises, elevating mean pulmonary artery pressure if cardiac output remains constant and therefore leading to increased pressure driving fluid out of the leaking capillaries. It is not until this vicious circle has flooded most of the lung that Q_S/Q_T rises and Pao$_2$ falls precipitously.

In these conscious animals myocardial blood flow was increased to all layers after 24 and 48 hours hyperoxia, in contrast to findings in anesthetized animals.[11,12] These increases can be explained as the natural consequence of a normally maintained C.O. in the face of elevated SVR leading to mild systemic hypertension. These findings may help explain the mechanism of reduction of infarct size by oxygen inhalation following acute coronary occlusion.[10] Prolonged hyperoxia does not significantly impair myocardial blood flow or alter its distribution in conscious dogs. Left ventricular dysfunction on the basis of ischemia during hyperoxia seems highly unlikely. More conclusively, direct monitoring of the central circulation in conscious dogs showed no evidence to support left ventricular failure on any basis in the pathogenesis of oxygen toxicity. The maintenance of a normal cardiac output in the face of an increased SVR and a decreased left atrial pressure excludes left ventricular dysfunction as a factor in oxygen toxicity.

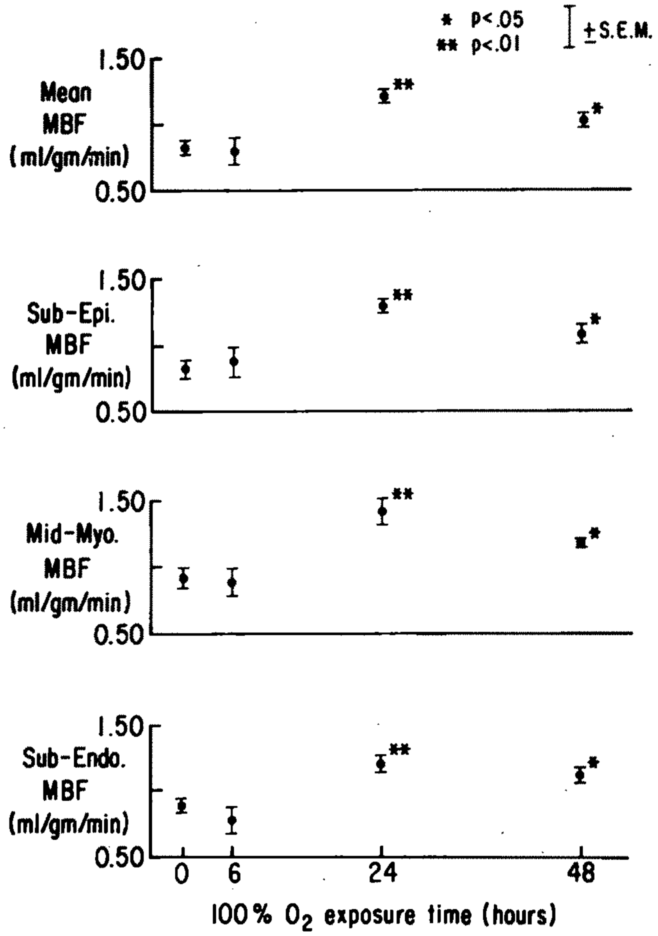


FIG. 6. Quantitative left ventricular blood flow (Mean MBF) and regional left ventricular blood flow to the sub-epicardial (Sub-Epi MBF), mid-myocardial (Mid-Myo MBF), and the sub-endocardial (Sub-Endo MBF) layers in Awake dogs are plotted against length of exposure time to hyperoxia. p values denote significance of changes from pre-exposure values.

In summary, prolonged hyperoxia in dogs causes interstitial pulmonary edema secondary to direct pulmonary capillary endothelial cell damage and *not* left ventricular failure. Any elevation of pulmonary capillary pressure is caused by obstruction of the pulmonary vascular bed by interstitial edema, and is *not* a reflection of rising left atrial pressure. Finally, prolonged hyperoxia causes small but uniform increases in total and regional left ventricular perfusion.

References

1. Barber, R. E., Lee, J. and Hamilton, W. K.: Oxygen Toxicity in Man. N. Eng. J. Med., 283:1478, 1970.
2. Barratt-Boyes, B. G. and Wood, E. H.: Cardiac Output and Related Measurements and Pressure Values in the Right Heart and Associated Vessels, Together with an Analysis of the Hemodynamic Response to the Inhalation of High Oxygen Mixtures in Healthy Subjects. J. Lab. Clin. Med., 51:72, 1958.
3. Caldwell, P. R. B., Lee, W. L., Jr., Schildkraut, H. S. and Archibald, E. R.: Changes in Lung Volume, Diffusing Capacity, and Blood Gases in Men Breathing Oxygen. J. Appl. Physiol., 21:1477, 1966.
4. Cropp, G. J. A.: Effect of High Intra-alveolar Oxygen Tensions on Pulmonary Circulation in Perfused Lungs of Dogs. Am. J. Physiol., 208:130, 1965.
5. Domenech, R. J., Hoffman, J. I. E., Noble, M. I. M., et al.: Total and Regional Coronary Blood Flow Measured by Radioactive Microspheres in Conscious and Anesthetized Dogs. Cir. Res., 25:581, 1969.
6. Kapanci, Y., Weibel, E. R., Kaplan, H. P. and Robinson, F. R.: Pathogenesis and Reversibility of the Pulmonary Lesions of Oxygen Toxicity in Monkeys. II. Ultrastructural and Morphometric Studies. Lab. Invest., 20:101, 1969.
7. Kaplan, H. P., Robinson, F. R., Kapanci, Y. and Weibel, E. R.: Pathogenesis and Reversibility of the Pulmonary Lesions of Oxygen Toxicity in Monkeys. I. Clinical and Light Microscopic Studies. Lab. Invest., 20:94, 1969.
8. Kistler, G. S., Caldwell, P. R. B. and Weibel, E. R.: Development of Fine Structural Damage to Alveolar and Capillary Lining Cells in Oxygen-Poisoned Rat Lungs. J. Cell. Biol., 33:605, 1967.
9. Liland, A. E., Zapol, W. M. Qvist, J., et al.: Positive Airway Pressure in Lambs Spontaneously Breathing Air and Oxygen. J. Surg. Res., 20:85, 1976.
10. Maroko, P. R., Radvany, P., Braunwald, E. and Hale, S. L.: Reduction of Infarct Size by Oxygen Inhalation Following Acute Coronary Occlusion. Circulation, 52:360, 1975.
11. Marshall, R. J., Parratt, J. R. and Ledingham, I. McA.: The Effect of Hyperbaric Oxygen (2 ATA) on Myocardial Blood Flow and Oxygen Consumption in Normal and Ischemic Areas of Myocardium After Acute Coronary Artery Ligation in the Dog. *In* Trapp, W. G., Bannister, E. W., Davison, A. J. and Trapp, P. A. (eds.) O_2 5th International Hyperbaric Congress Proceedings, Simon Fraser University, Barnaby, British Columbia, 1974.
12. Pelled, B., Seki, Y., Ramsey, F. and Lambertsen, C. J.: Effects of Hyperoxia on the Coronary Circulation and Myocardial Function. *In* Trapp, W. G., Bannister, E. W., Davison, A. J. and Trapp, P. A. (eds.) O_2 5th International Hyperbaric Congress Proceedings, Simon Fraser University, Burnaby, British Columbia, 1974.
13. Singer, M. M., Wright, F., Stanley, L. K., et al.: Oxygen Toxicity in Man. N. Engl. J. Med., 283:1473, 1970.
14. Van De Water, J. M., Kagey, K. S., Miller, I. T., et al.: Response of the Lung to Six to Twelve Hours of 100 Per Cent Oxygen Inhalation in Normal Man. N. Engl. J. Med., 283:62, 1970.
15. Vatner, S. F. and Braunwald, E.: Cardiovascular Control Mechanisms in the Conscious State. N. Engl. J. Med., 293:970, 1975.
16. Wittner, M. and Rosebaum, R. M.: Pathophysiology of Pulmonary Oxygen Toxicity. *In* Brown, I. W. Jr. and Cox, B. G. (eds.) Proceedings of the 3rd International Conference on Hyperbaric Medicine, (Washington, Nat. Acad. Sci., 1966).
17. Wolfe, W. G. and DeVries, W. C.: Oxygen Toxicity. Ann. Rev. Med., 26:203, 1975.
18. Wolfe, W. G., DeVries, W. C., Anderson, R. W. and Sabiston, D. C., Jr.: Changes in Pulmonary Capillary Filtration and Ventilatory Dead Space During Exposure to 95% Oxygen. J. Surg. Res., 16:312, 1974.
19. Wolfe, W. G. and Sabiston, D. C., Jr.: Lung Function in Spontaneously Breathing and Mechanically Ventilated Dogs Exposed to 95% Oxygen. Surg. Gynecol. Obstet., 137:763, 1973.
20. Wood, C. D. and Perkins, G. F.: Blood Pressure Responses to Oxygen Toxicity. *In* Trapp, W. G., Bannister, E. W., Davison, A. J. and Trapp, P. A. (eds.) O_2 5th International Hyperbaric Congress Proceedings, Simon Fraser University, Burnaby, British Columbia, 1974.
21. Wood, C. D., Perkins, G. F., Smith, A. G. and Reaux, J. M.: Response of the Cardiovascular System in Oxygen Toxicity. Aerospace Med., 43:162, 1972.

Autotransplantation of Pancreatic Fragments to the Portal Vein and Spleen of Totally Pancreatectomized Dogs:

A Comparative Evaluation

GEORGE J. KRETSCHMER, M.D.,* DAVID E. R. SUTHERLAND, M.D., ARTHUR J. MATAS, M.D., WILLIAM D. PAYNE, M.D., JOHN S. NAJARIAN, M.D.

From the Department of Surgery, University of Minnesota Health Sciences Center, Minneapolis, Minnesota

Forty-nine dogs were made diabetic by total pancreatectomy. Fifteen untreated pancreatectomized animals survived a mean (±S.E.) of 7.0 ± 1.1 days with a mean (±S.E.) plasma glucose level of 402 ± 26 mg/100 ml before death. The pancreata of 32 dogs were distended with cold (4°) Hanks' solution, minced, digested with collagenase (600 U/ml tissue) for 15–25 minutes, and autotransplanted either into the splenic artery (three dogs), directly into the splenic pulp (21 dogs), or into the portal vein (ten dogs). Tissue infusion into the splenic artery resulted in infarction and persistent hyperglycemia. Direct implantation into the splenic pulp of tissue digested for 15, 20 and 25 minutes resulted in permanent normoglycemia (fasting plasma glucose < 150 mg/100 ml) in 7 of 8, 7 of 7, and 6 of 6 dogs respectively. Glucose tolerance test mean (±S.E.) K values (% decline of plasma glucose concentration/minute) in these groups two weeks after transplantation were 1.20 ± 0.20%, 1.60 ± 0.25 and 0.70 ± 0.08% respectively, indicating that 20 minutes digestion was best for intrasplenic transplantation. Tissue prepared in the optimal manner (20 minutes digestion) and embolized into the liver resulted in normoglycemia in three of eight dogs, and a mean (±S.E.) K value of 0.77 ± 0.10%. Both dogs receiving tissue dispersed for 25 minutes into the portal vein remained hyperglycemic. In the dogs subjected to intraportal transplantation, portal pressure rose from a mean (±S.E.) of 6.5 ± 0.6 cm H_2O before to 21.9 ± 2.2 cm H_2O immediately after tissue embolization, but declined to 6.5 ± 1.0 cm H_2O by ten weeks in animals becoming normoglycemic. We conclude that in dogs direct implantation of pancreatic tissue into the splenic pulp is superior to embolization into the portal vein or splenic artery because the splenic circulation is not compromized, portal hypertension is obviated, and glucose metabolism is best controlled as judged by glucose tolerance test K values.

THE RESULTS OF ISLET transplantation experiments in rats indicate that embolizing the tissue into the portal vein is an effective technique, and that fewer islets are required to ameliorate the diabetic state then when other sites are used.[1,6,10,23] Low islet yield is a major obstacle to successful transplantation of isolated islets of Langerhans in large animals,[11,19,22] as well as in man.[18] Therefore, it is important to utilize the available islets as efficiently as possible by transplantation to the most favorable site.

Mirkovitch and associates[13] first showed that dispersed pancreatic tissue, prepared by collagenase digestion without separation of exocrine and endocrine components, could ameliorate diabetes when transplanted to totally pancreatectomized dogs. We have confirmed the feasibility of this approach,[8] but found that complete normalization of carbohydrate metabolism, as judged by glucose tolerance tests, was not achieved by intrasplenic transplantation. Furthermore, even though elimination of the steps required for specific islet isolation was designed to minimize islet loss, we found that the majority of islet tissue was destroyed during the period of collagenase digestion necessary to effectively disperse the pancreas.

In this report we describe our search to determine whether the spleen or the liver provides the best site for implantation of dispersed pancreatic tissue in pancreatectomized dogs. Both sites possess the theoretical advantage of allowing secreted insulin to percolate through the liver before it enters the systemic circulation. However, because we purposely omitted islet purification, each procedure carried potential dangers —portal hypertension and impairment of liver function

---

* Current address: G. J. Kretschmer, M.D., I. Surgical University Clinic, Alser Strasse 4, A-1097-Vienna, Austria.

Correspondence and reprint requests: Dr. Sutherland, Box 253 Mayo Memorial Building, University of Minnesota Hospitals, 420 Delaware Street S.E., Minneapolis, Minnesota 55455.

Supported by USPHS grant AM16566 and grants from the American Diabetes Association, Minnesota Chapter and the Juvenile Diabetes Foundation. Dr. Kretschmer is the recipient of a research scholarship from the Max Kade Foundation, Inc., New York. Dr. Sutherland is the recipient of USPHS Research Career Development Award 1K04 AM00161.

Submitted for publication: April 4, 1977.

0003-4932-78-0100-0079-0085 © J.B. Lippincott Company

when the tissue is embolized via the portal vein, and hemorrhage or vascular compromise when transplanted to the spleen.

Materials and Methods

Animals

Seventy-one mongrel dogs were used in the experiments. Twenty-two dogs did not undergo operation and constituted the normal control group for establishment of normal fasting plasma glucose levels and normal intravenous glucose tolerance test curves.

Forty-nine dogs were totally pancreatectomized according to the technique of Markowitz[9] leaving the duodenum *in situ*. Fifteen of these dogs were not further treated, and served as apancreatic control animals. The remaining 34 dogs were divided into the experimental groups and received autotransplants of pancreatic tissue.

Tissue Preparation and Analysis

Each pancreas was distended *in situ* by cannulating the pancreatic duct and injecting cold (4°) Hanks' solution containing 8.5 mg/100 ml of aprotinin (Trasylol, FBA Pharmaceuticals) and then rapidly excised (15–25 minutes). The entire pancreas was minced in a mechanical tissue chopper[11] into fragments with a maximal diameter of 1.4 mm (able to pass through a 15 guage needle). The minced tissue was washed three times by sedimentation for three minutes in cold Hanks' solution. The settled volume of tissue after mincing was approximately 1 ml for each 0.4 g wet weight of pancreas, and the total volume ranged from 50 to 120 ml per pancreas (mean of 85 ± 4 (S.E.) ml). The minced tissue was digested at 37° in a shaking water bath with 600 units collagenase (Worthington Type IV)/ml of tissue for 15, 20 or 25 minutes. After digestion, the tissue was washed four times by sedimentation for three minutes in cold Hanks' solution. The settled volume of tissue recovered after digestion ranged from 20 to 70 ml per pancreas after 15 minutes of digestion (mean of 41 ± 6 (S.E.) ml), from 10 to 55 ml after 20 minutes of digestion (mean of 31 ± 45 (S.E.) ml) and from 15 to 35 ml after 25 minutes of digestion (mean of 25 ± 3 (S.E.) ml). The maximal diameter of the tissue particles after digestion was 0.6 mm and the digested tissue was able to pass through a 20 gauge needle. The digested tissue from each pancreas was resuspended in 20–70 ml of cold Hanks' solution and aspirated into a syringe for implantation into recipient animals.

The attritions of islet tissue and exocrine pancreas digestive enzymes were determined by measuring the insulin and amylase content of tissue aliquots obtained during each step of processing. The calculations were performed on the basis of previous findings that tissue insulin and amylase content are proportional to pancreatic beta cell mass and exocrine enzyme concentrations, respectively.[21] Insulin was measured by the double antibody radioimmunoassay technique of Morgan and Lazarow,[15] using porcine insulin standards. Amylase was measured by the coloriometric technique of Jamison et al.,[4] using hog pancreatic alpha amylase as the standard.

Experiment Groups and Techniques of Transplantation

Direct implantation into the splenic pulp. Twenty-one pancreatectomized dogs received pancreatic tissue by direct implantation into the splenic pulp. This site was used to determine the optimal length of collagenase digestion for tissue dispersal. Eight animals were transplanted with tissue digested for 15 minutes, seven for 20 minutes, and six for 25 minutes. In each recipient the splenic vessels and short gastric vessels were occluded with vascular clamps, the splenic capsule was punctured with a long catheter (I.D. 2 mm) directed from the upper to the lower pole, and the tissue was injected as the catheter was slowly withdrawn. The site of capsular injury was then oversewn, the clamps were removed, and the splenic circulation was reestablished.

Embolization into the splenic artery. In three pancreatectomized dogs, tissue digested for 20 minutes was injected via the splenic artery. The splenic artery was punctured near the hilum of the spleen and branches to other structures were temporarily occluded while the tissue was embolized into the spleen. Hemostasis was achieved with a single vascular suture.

Embolization into the portal vein. Tissue was embolized to the liver of ten pancreatectomized dogs by injection into the portal vein. Eight animals were transplanted with tissue digested for 20 minutes. Because of the desirability of reducing the quantity of tissue injected, two dogs received tissue digested for 25 minutes. Heparin (100 units/kg body weight) was given systemically just prior to tissue implantation. Portal vein pressures and inferior vena cava pressures were measured before, during and immediately after slow injection of tissue through a mesenteric vein.

Survival and Metabolic Studies

Total pancreatectomy in dogs induces hyperglycemia, glycosuria, and ketoacidosis and is uniformally lethal if untreated.[12,20] The duration of survival is a valuable measure of transplant function. The number of days of survival after pancreatectomy were determined for untreated apancreatic control dogs and for recipients of an islet transplant. Mean duration of survival was calculated for apancreatic control dogs and for transplanted dogs who remained hyperglycemic.

Fasting plasma glucose concentrations were determined in all dogs before pancreatectomy, daily for two weeks after operation, and weekly thereafter in surviving dogs. Additional glucose determinations were done in transplanted dogs immediately after pancreatectomy and four hours after transplantation. Plasma glucose concentrations were measured with the glucose oxidase method,[5] using a Beckman autoanalyzer. Normoglycemia was defined as a plasma glucose of <150 mg/100 ml after a 12 hour fast.

Intravenous glucose tolerance tests were performed on six apancreatic control dogs who were alive seven days after pancreatectomy, and on 23 normoglycemic dogs 14 days after transplantation. For glucose tolerance tests, 0.5 g of glucose per kg of body weight was administered, blood samples were collected before injection (0 minutes), and at 10, 20, 30, 60, 90 and 120 minutes thereafter. A K value (% decline of plasma glucose concentration per minute) was calculated for each dog from the 10, 20, and 30 minute postinjection plasma glucose values, according to the method of Moorehouse et al.[14] Blood biochemistry values (serum bilirubin, glutamic oxalacetic transaminase (SGOT), alkaline phosphatase, and lactic acid dehydrogenase [LDH]) were measured before transplantation, and two to four days and four weeks after transplantation.

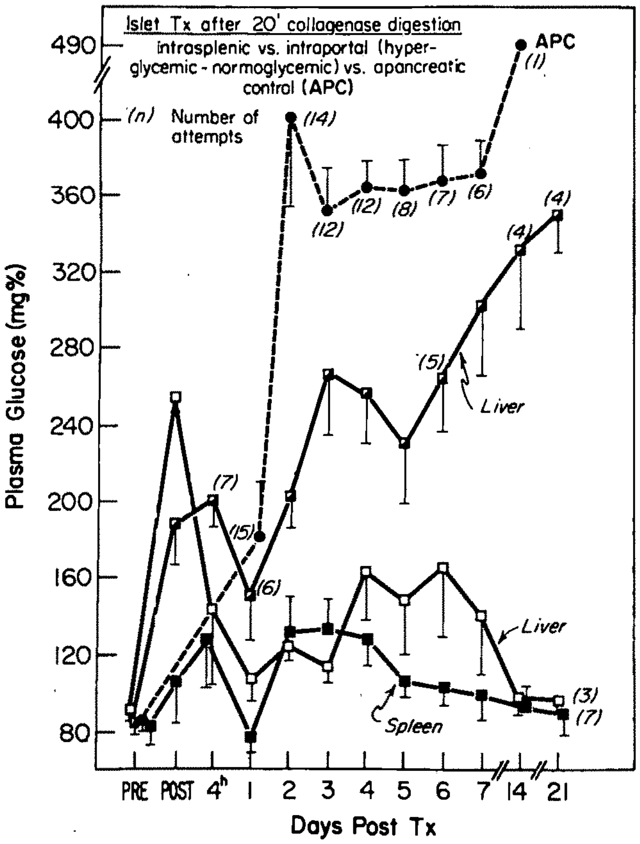


FIG. 1. Serial fasting plasma glucose levels (mean ± S.E.) in apancreatic dogs and in pancreatectomized dogs receiving tissue (20 minutes digestion) into the splenic pulp or into the liver via the portal vein. The values are plotted separately for dogs becoming normoglycemic and those remaining hyperglycemic after intraportal transplantation.

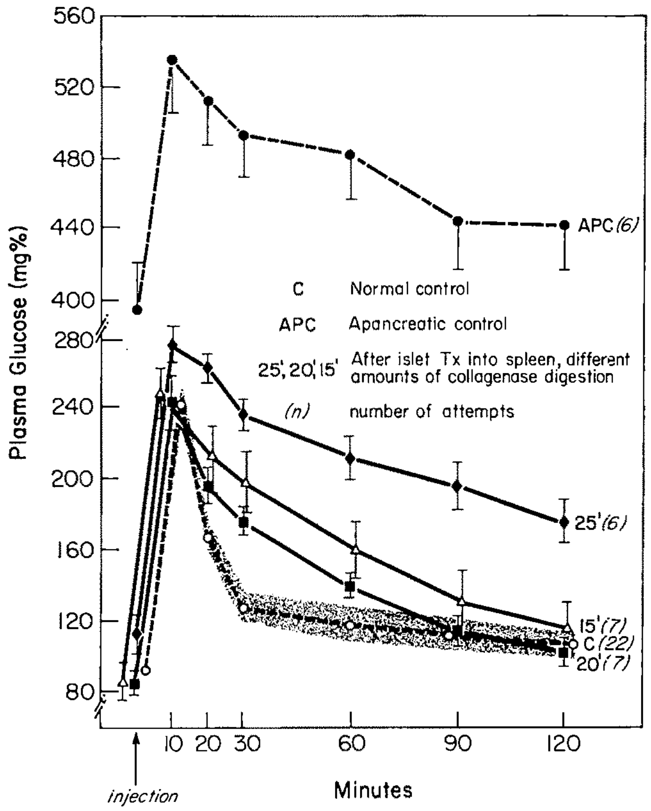


FIG. 2. Comparative intravenous glucose tolerance test curves at two weeks in pancreatectomized autograft recipients of tissue digested for 15, 20 or 25 minutes, in apancreatic dogs, and in normal control dogs. Values are expressed as mean ± S.E.

Ten weeks after transplantation, laparotomies were performed on three normoglycemic dogs who had received islet tissue into the portal vein, and their portal and inferior vena cava pressures were remeasured. Splenectomies were performed on 12 normoglycemic recipients of islet tissue implanted into the splenic pulp. Daily plasma glucose levels and the mean survival after splenectomy were determined.

Results

Survival and Metabolic Studies

Apancreatic control dogs. All 15 apancreatic control dogs died between two and 15 days after operation (mean survival 7.0 ± 1.1 (S.E.) days). Fasting serum glucose levels rose immediately after pancreatectomy and remained elevated (mean plasma glucose 401 ± 5 (S.E.) mg/100 ml on day 2) until death occurred (Fig. 1).

TABLE 1. *Incidence of Normoglycemia and K Values in Pancreatectomized Dogs According to Technique of Transplantation*

Length of Collogenase Digestion	Implant Site	No. of Recipients	No. Becoming Normo-glycemic	GTT* K values ± S.E.†
15′	Splenic Pulp	8	7	1.20 ± 0.20%
20′	Splenic Pulp	7	7	1.60 ± 0.25%
25′	Splenic Pulp	6	6	0.78 ± 0.08%
20′	Splenic Artery	3	0	—
20′	Portal Vein	8	3	0.77 ± 0.10%
25′	Portal Vein	2	0	—

* Glucose tolerance test

† Normal K value: 3.30 ± 0.2% (22 dogs)

Glucose tolerance test curves performed at one week were distinctly abnormal (Fig. 2). Mean K value in apancreatic control dogs was 0.35 ± 0.05 (S.E.) mg/100 ml, significantly less than the mean K value of 3.30 ± 0.27 (S.E.) mg/100 ml in 22 normal dogs ($p < 0.001$). Residual pancreatic fragments were not found in any pancreatectomized dogs at autopsy, confirming the functional apancreatic state.

Recipient dogs. The incidence of successful transplantation, *i.e.*, induction of permanent normoglycemia (fasting plasma glucose < 150 mg/100 ml), for each group of animals, is summarized in Table 1. Twenty of the 21 pancreatectomized dogs receiving tissue implanted directly in the splenic pulp became normoglycemic. However, tissue digested for 20 minutes gave the best results, as seen by the glucose tolerance curves (Fig. 2) and K values (Table 1). The 7 dogs receiving tissue prepared by digestion for 20 minutes became normoglycemic immediately after transplantation (Fig. 1). The 12 normoglycemic recipients of tissue implanted into the splenic pulp who were subjected to splenectomy at ten weeks became hyperglycemic immediately after operation, and died between one and 15 days. Mean survival after splenectomy was 4.1 ± 1.4 (S.E.) days and mean plasma glucose concentration one day prior to death was 312 ± 24 mg/100 ml.

The good results after implanting pancreatic tissue directly into the splenic pulp are in direct contrast to the poor results of embolizing the tissue into the splenic artery. All three recipients of tissue (optimally digested for 20 minutes) infused into the splenic artery remained hyperglycemic, and survived 7, 11, and 21 days. Mean plasma glucose concentration at death was 438 ± 43 (S.E.) mg/100 ml. Postmortem examination of the two dogs with the shortest survival showed multiple splenic infarcts of various size, although the main splenic artery was patent.

Embolization into the portal vein of pancreatic tissue dispersed for 20 minutes produced normoglycemia in three of eight recipients. Although plasma glucose levels in these three animals were reduced immediately after transplantation, a longer period was required before their levels remained below 150 mg/100 ml, which stands in contrast to those dogs receiving tissue into the splenic pulp (Fig. 1). Five dogs who received tissue digested for 20 minutes into the portal vein remained hyperglycemic (Fig. 1), and died between one and 65 days (mean survival 25.2 ± 11.3 (S.E.) days). Because we thought that reduction in the bulk of tissue transplanted might provide an advantage for transplantation via the portal vein, we gave two pancreatectomized dogs intraportal injections of tissue digested for 25 minutes. Both of these recipients remained hyperglycemic and survived for eight and 38 days respectively.

Glucose tolerance test curves 14 days after transplantation in the three normoglycemic recipients of tissue embolized into the portal vein were clearly abnormal (Fig. 3), indicating that these dogs had a decreased carbohydrate tolerance when compared to pancreatectomized dogs receiving tissue digested for 20 minutes into the splenic pulp. Evaluation of the differences in K values between these two groups (Table 1) by student's t test results in a p value of <0.07.

An increase in portal vein pressure occurred in all dogs receiving tissue into the portal vein. Their portal pressures rose from a preinfusion mean of 6.1 ± 1.0 (S.E.) cm H_2O to 21.9 ± 2.2 (S.E.) cm H_2O immediately after infusion. The initial rise in portal pressure in the three dogs becoming normoglycemic was no different than in the dogs who remained hyperglycemic (Table 2). However, ten weeks after transplantation mean portal pressure of these three animals had de-

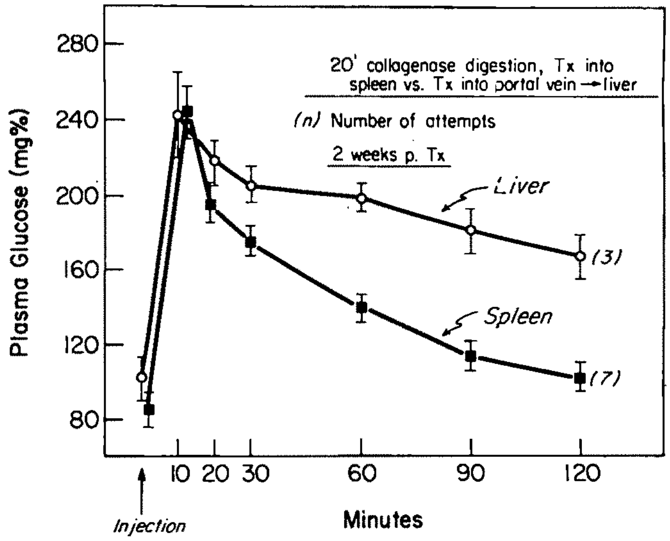


FIG. 3. Comparative intravenous glucose tolerance test curves at two weeks in pancreatectomized dogs becoming normoglycemic after autotransplantation of tissue (20 minutes digestion) to the liver or the spleen. Values are expressed as mean ± S.E.

clined to pretransplant levels; the induction of portal hypertension was not permanent.

The results of blood biochemistry values in recipients of intraportal and intrasplenic transplants are compared in Figure 4. The mean SGOT and alkaline phosphatase concentrations rose slightly in dogs receiving tissue into the spleen. Mean serum LDH concentrations of both groups of dogs more than doubled by two weeks after transplantation, but by four weeks the values approached pretransplant levels. Serum bilirubin levels did not change in dogs receiving tissue into the spleen; a transient, but insignificant ($p > 0.2$) rise, occurred in dogs receiving tissue into the portal vein. The mean SGOT concentration rose more than four-fold during the first three days in dogs receiving tissue into the portal vein ($p < 0.02$), but returned to just above the normal level by four weeks. However, alkaline phosphatase levels increased and remained significantly elevated at four weeks ($p < 0.02$). The blood biochemistry profiles of the three recipients that became normoglycemic after transplantation into the portal vein were not different than those observed in the dogs that remained hyperglycemic.

Insulin and Amylase Content of Pancreatic Tissue

The results of transplantation were correlated with the *in vitro* analyses of insulin and amylase content of the transplanted tissue. Approximately 50% of the insulin and amylase content was lost by mincing (Table 3). As expected, collagenase digestion resulted in a progressive loss of tissue insulin content. Although with 15 minutes collagenase digestion, 18 ± 6 (S.E.)% of the original insulin content was recovered, and with 20 minutes digestion only 8 ± 2 (S.E.)% was recovered, the results of intrasplenic transplantation were better with the latter protocol, indicating that the degree of tissue dispersal was important. However, an optimal balance existed between the extent of dispersal and the amount of islet tissue recovered, since tissue digested for 25 minutes (6 ± 3 (S.E.)% recovery) and transplanted to the spleen resulted in a less complete amelioration of the diabetic state.

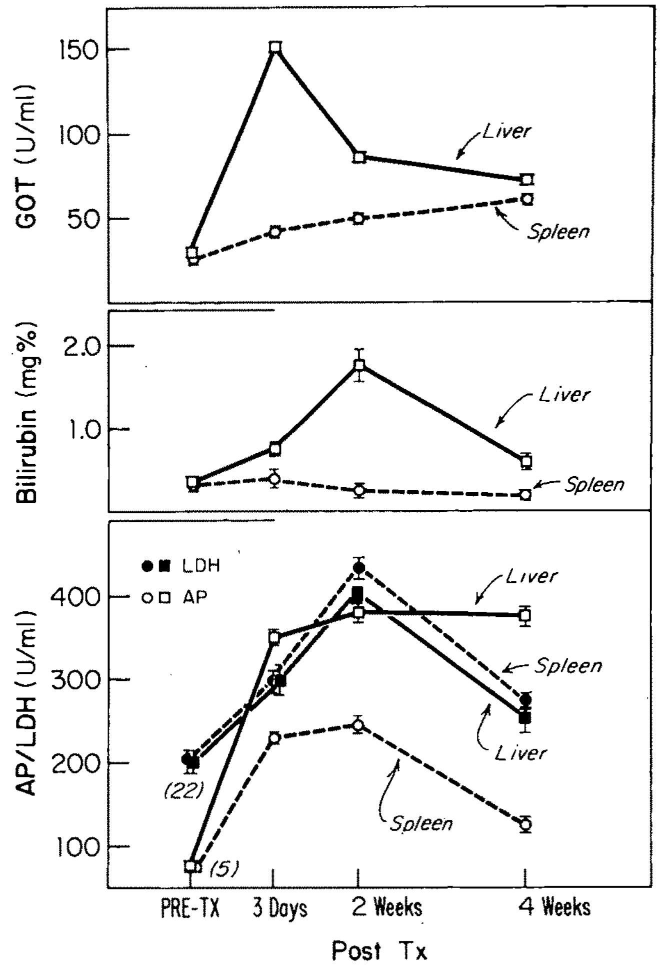


FIG. 4. Blood biochemistry values (mean ± S.E.) before and serially after pancreatectomy and pancreatic tissue autotransplanted to the liver and spleen.

The decrease in total tissue amylase content was proportionately more than the decrease of insulin content during tissue processing, resulting in approximately a 50% increase of tissue insulin/amylase ($p < .05$) ratio, indicating that a small degree of purification from exocrine enzymes occurred.

TABLE 2. *Portal Pressure Before, Immediately After, and Ten Weeks After Transplantation via the Portal Vein*

	Mean Portal Pressure (cm H_2O ± S.E.)		
		Posttransplant	
Outcome of Transplant	Pretransplant	Immediate	10 Weeks
Normoglycemic (n = 3) (20′ digestion)	6.2 ± 0.9	27.8 ± 1.6	6.5 ± 1.0
Hyperglycemic (n = 5) (20′ digestion)	5.9 ± 0.9	21.2 ± 2.2	—
Hyperglycemic (n = 2) (25′ digestion)	6.5 ± 1.5	22.5 ± 3.0	—

TABLE 3. *Total Insulin and Amylase Content and Insulin/Amylase (I/A) Ratio of Pancreatic Tissue Before and After Processing**

	Insulin μg/pancreas	Per cent Recovery	Amylase mg/pancreas	Per cent Remaining	I/A† Ratio
Whole Pancreas (n = 34)	2352 ± 254	100	302 ± 27	100	11 ± 1
After Mincing (n = 34)	1325 ± 130	54 ± 6	110 ± 10	43 ± 3	13 ± 2
After Collagenase Digest					
15′ (n = 8)	241 ± 72	18 ± 6	20 ± 6	9 ± 3	16 ± 3
20′ (n = 18)	145 ± 26	8 ± 2	12 ± 3	9 ± 4	16 ± 3
25′ (n = 7)‡	103 ± 43	6 ± 2	6 ± 1	5 ± 2	16 ± 8

* Values expressed as Mean ± S.E.
† μg insulin/mg amylase.
‡ Tissue analysis could not be performed on one pancreas in the 25′ group.

We also compared the recovery of tissue insulin and amylase content after 20 minutes of digestion between the dogs receiving tissue into the spleen and the dogs receiving tissue into the portal vein. The mean insulin content of the tissue transplanted to the portal vein (115 ± 36 (S.E.) μg) was less than the mean insulin content of tissue transplanted to the spleen (156 ± 37 (S.E.) μg), but the differences were not statistically significant ($p > 0.2$). Likewise, there was not a significant difference between the insulin and amylase content of the tissue (20 minutes digestion) transplanted to the portal vein of the recipients that became normoglycemic and those that remained hyperglycemic.

Discussion

Successful transplantation of dispersed pancreatic tissue depends upon the same factors that are essential for free grafting of other endocrine tissue:[20] (a) the method of tissue preparation must conserve a critical mass of tissue; (b) the fragments must be of appropriate size to survive by nutrient diffusion until neovascularization occurs; and (c) the site of implantation must be appropriate.

Preparation of pancreatic islet tissue basically depends upon a combination of mechanical and enzymatic dispersal. We found that a continual loss of both endocrine and exocrine components (as estimated by tissue insulin and amylase content) occurred during all steps of tissue processing. Theoretically, the recovery of a larger amount of endocrine tissue should improve the results of transplantation. By mincing only, approximately 50% of the tissue insulin content can be recovered. However, if collagenase digestion is omitted from the dispersal procedure, pancreatectomized dogs respond very poorly to intrasplenic implantation of pancreatic tissue.[8] Collagenase digestion for 20 minutes results in the most rapid occurrence of normoglycemia after transplantation, and gives the best glucose tolerance test results, even though islets are lost during the process of tissue preparation.

Although we made no specific attempt to purify islets from exocrine tissue, there was some increase in the insulin/amylase ratio. Attrition of exocrine enzyme content during collagenase digestion may be an important factor in tissue preparation. If we had attempted to isolate the islets after collagenase digestion, a further decrease in the quantity of islet tissue available for transplantation would probably have resulted. Deletion of this step maximized the yield and provided the proper balance between the degree of tissue dispersal, depletion of exocrine enzyme content, and islet recovery necessary for successful grafting of pancreatic fragments.

In regard to the appropriate site for transplantation of dispersed pancreatic tissue in dogs, our results indicate that the direct implantation into splenic pulp is superior to embolization into the portal vein or splenic artery. The splenic artery is clearly unsatisfactory because of the uniform failure to lower plasma glucose and because of the development of splenic infarcts.

The better results of islet transplantation into the splenic pulp as compared to embolization into the portal vein is somewhat at variance with the observations in rats. In rats, islet embolization into the liver by injection into the portal vein increases the efficiency of islet transplantation,[1,6,10,23] and does not induce liver damage.[1] Koncz et al. obtained less good results by islet transplantation into the spleen of diabetic rats,[7] but a comparative evaluation in these species has not been published. From our own experience in diabetic rats, transplantation of dispersed neonatal pancreas into the portal vein results in a higher cure rate than with transplantation into the spleen (unpublished observations). However, in the dog the situation seems to be reversed. One possible explanation for these differences stems from the observations that the mean insulin content of the tissue (20 minutes digestion) that we transplanted to the portal vein was lower than the insulin content of tissue (20 minutes digestion) transplanted directly into the spleen. However, the differences in final tissue insulin content were not statistically significant between these groups; there was extreme variability in tissue insulin recovery (as reflected by the large standard errors), and the insulin content was also low in some of the tissue preparations successfully transplanted to the spleen. In addition, the mean insulin content of the tissue digested for 20 minutes and transplanted to the portal vein was higher than the insulin content of the tissue digested for 25 minutes and successfully transplanted to the spleen. Therefore we do not think that the insignificant ($p > 0.2$) differences in tissue insulin recovery explains the poor results of transplantation via the portal vein.

A more likely explanation relates to the sensitivity of the dog liver to the insult of tissue embolization into the portal vein. Portal hypertension was a common sequela of islet transplantation into the portal vein of our dogs. We have noted an increase of portal pressure during infusion of pancreatic fragments decontaminated of exocrine enzymes by tissue culture for 24 hours.[11] In these earlier experiments, we discontinued the infusion when the portal pressure rose and we distributed the remaining tissue in the peritoneal cavity. However, in the experiments on transplantation of cultured tissue we employed a less reliable model of canine diabetes (partial pancreatectomy and administration of streptozotocin); therefore, the results of these previous investigations are difficult to interpret.

Other investigators have also used the portal vein of dogs. Mosimann et al.[17] did not even mention the problem of portal hypertension in their experiments with total pancreatectomy and infusion of collagenase digested tissue into the portal vein. They dispersed only the distal pancreas, and transplanted a smaller quantity of tissue than we did.

Portal hypertension was clearly a problem with our method of tissue preparation when the intraportal route of implantation was used. Although the portal hypertension was transient, at least in the dogs who survived in the normoglycemic state, we were unable to estimate exactly how much time was needed for the pressure to return to normal.

In addition to the hemodynamic problems associated with transplantation to the portal vein, blood biochemistry studies showed impairment of hepatic function when compared to animals receiving tissue directly into the splenic pulp. The elevation of bilirubin was minimal and insignificant, but the initial rise in SGOT was significant ($p < 0.02$) and had not returned entirely to normal by four weeks. Alkaline phosphatase levels remained elevated throughout the observation period of the dogs receiving tissue into the portal vein. Elevations of LDH were transient in all dogs. The slight derrangements in blood biochemistry values that we observed in the dogs receiving tissue into the spleen were probably related to the operative trauma itself, since the alterations were minimal when compared to the dogs who received tissue into the portal vein. It seems reasonable to conclude that embolization of large amounts of tissue into the portal vein of dogs impairs hepatic function. The liver abnormalities in the dogs that remained hyperglycemic may have been related to the persistance of the diabetic state and to insulin deficiency.[9,12]

We do not mean to imply that the portal vein is necessarily a poor site for transplantation. The good results with transplantation into the portal vein of rats have been obtained using either isolated adult islets[1,6,23] or dispersed neonatal pancreas.[10] The availability of inbred strains and of multiple donors makes these techniques easily applicable to rats. Transplantation of a purified islet preparation to the portal vein might be equally successful in dogs, but the difficulties with islet isolation will make this hypothesis difficult to test in an autograft model; and the lack of inbred strains precludes testing, without complicated immunological maneuvers to eliminate the variability of rejection, in an allograft model. The hypothesis may be testable in rats. In preliminary experiments, we have transplanted isologous adult rat pancreatic fragments (dispersed by collagenase digestion without islet isolation) to the portal vein of diabetic rats and ameliorated diabetic state in three of 41 trials (unpublished observations). We have not transplanted comparably prepared tissue to the spleen of diabetic rats, but such an experiment would establish whether or not the spleen, as a recipient site, is more receptive to unpurified pancreatic tissue than the portal vein in a species other than the dog.

We also do not intend that our observations be extrapolated to the clinical situation. Certainly the portal pressure should be monitored closely during infusion of islet tissue into the portal vein, but in our preliminary experience with islet transplantation in humans, infusion of a small quantity of tissue into the portal vein was not associated with elevation of portal pressure or deterioration of hepatic function.[18]

The results of our experiments indicate that the spleen is a favorable site for transplantation of unpurified pancreatic islet tissue in dogs. Implantation of islets into the spleen combines the physiological benefits of direct secretion of insulin into the portal circulation (analogous to the normal situation) with the ability to transplant a large amount of pancreatic tissue without islet purification. Portal hypertension is obviated and the splenic circulation is not compromized. In addition, the extreme vascularity of the spleen favors the survival of freshly implanted tissue.

From an experimental point of view, transplantation into the spleen is attractive. In our normoglycemic dogs with grafted tissue in the splenic pulp, splenectomy lead to recurrence of the hyperglycemic state and death within approximately the same time as after pancreatectomy. These experiments conclusively demonstrated the dependence upon the transplanted tissue and proved that the original pancreatectomy was complete.

The dog and human spleen differ anatomically and may also differ in their response to injury. Nevertheless, the feasibility of repairing or conservatively treating splenic injury in humans has been demonstrated,[3,16] which suggests that the human spleen could withstand the stress of islet transplantation. Although other questions remain to be answered, including the fate of allogenic tissue implanted within the spleen (an immunological organ), the spleen should be considered as an appropriate recipient site for clinical islet transplant trials.

Acknowledgments

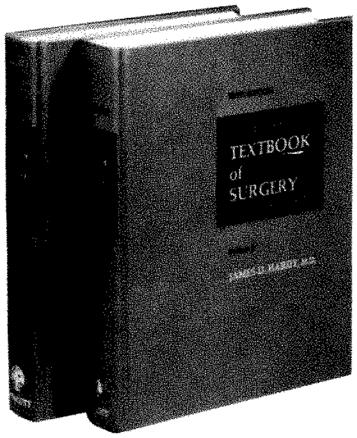
We are grateful to Thomas L. Cain, Les Olson, Elizabeth Frenzel, Phyllis Gorecki, June Eckhardt and Ann Lowe for their technical assistance and to Janet Sanders for her help in the preparation of this manuscript.

References

1. Amamoo, D. G., Woods, J. E. and Holley, K. E.: Effect of Intrahepatically Transplanted Islets of Langerhans on Hepatic Function in the Rat. Mayo Clin. Proc., 50:416, 1975.
2. Brooks, J. R.: Endocrine Tissue Transplanation. Springfield, Charles C. Thomas, 1962, pp. 83–85.

3. Febri, P. J., Metz, E. N., Nick, W. V. and Zollinger, R. M.: A Quarter Century with Splenectomy: Changing Concepts. Arch. Surg., 108:569, 1974.
4. Jamieson, A. D., Pruitt, K. M. and Caldwell, R. C.: An Improved Amylase Assay. J. Dent. Res., 48:483, 1969.
5. Kadish, A. H., Little, R. L. and Sternberg, J. C.: A New and Rapid Method for Determination of Glucose by Measurement of Rate of Oxygen Consumption. Clin. Chem., 114:116, 1968.
6. Kemp, C. B., Knight, M. J., Scharp, D. W., et al.: Effect of Transplantation Site on Results of Pancreatic Islets Isografts in Diabetic Rats. Diabetelogia, 9:486, 1973.
7. Koncz, L., Zimmerman, C. E., Dellelis, R. A. and Davidoff, F.: Transplantation of Pancreatic Islets into the Spleen of Diabetic Rats and Subsequent Splenectomy. Transplantation, 21:427, 1976.
8. Kretschmer, G. J., Sutherland, D. E. R., Matas, A. J., et al.: Autotransplantation of Pancreatic Islets Without Separation of Exo- and Endocrine Tissue in Totally Pancreatectomized Dogs. Surgery, 82:74, 1977.
9. Markowitz, J.: Experimental Surgery. Williams and Wilkins, Baltimore, 1959, pp. 342–363.
10. Matas, A. J., Sutherland, D. E. R., Steffes, M. W. and Najarian, J. S.: Islet Transplantation Using Neonatal Rat Pancreata: Quantitative Studies. J. Surg. Res., 20:143, 1976.
11. Matas, A. J., Sutherland, D. E. R., Steffes, M. W. and Najarian, J. S.: Short Term Culture of Adult Pancreatic Fragments for Purification and Transplantation of Islets of Langerhans. Surgery, 80:183, 1976.
12. Mering, J. and Minkowski, O.: Diabetes mellitus nach Pankreasexstirpation. Arch. Pharmakol. Exp. Pathol., 26:371, 1890.
13. Mirkovitch, V. and Campiche, M.: Successful Intrasplenic Autotransplantation of Pancreatic Tissue in Totally Pancreatectomized Dogs. Transplantation, 21:265, 1976.
14. Moorhouse, J. A., Grahame, G. R. and Rosen, N. J.: Relationship Between Intravenous Glucose Tolerance and Fasting Blood Glucose Level in Healthy and in Diabetic Subjects. J. Clin. Endocrinol., 24:145, 1964.
15. Morgan, C. R. and Lazarow, A.: Immunoassay of Insulin: Two antibody System. Plasma Insulin Levels of Normal, Subdiabetic and Diabetic Rats. Diabetes, 12: 115, 1963.
16. Morgenstern, L: Microcrystalline Collagen Used in Experimental Splenic Injury: A New Surface Hemostatic Agent. Arch. Surg., 109:44, 1974.
17. Mosimann, R., Rausis, C. and Mirkovitch, V.: Prevention du Diabete Chez Le Chien Pancreatectomise Par Autotransplantation De Tissu Pancreatique Dans Le Foie. Helv. Chir. Acta., 43:241, 1976.
18. Najarian, J. S., Sutherland, D. E. R., Matas, A. J., et al.: Human Islet Transplantation: A Preliminary Report. Transpl. Proc., 9:233, 1977.
19. Scharp, D. W., Murphy, J. J., Newton, W. T., et al.: Transplantation of Islets of Langerhans in Diabetic Rhesus Monkeys. Surgery, 77:100, 1975.
20. Sirek, A.: Pancreatectomy and Diabetes. In Pfeiffer, E. F., et al. (eds.): Handbook of Diabetes Mellitus (Vol. 1), Lehmann's Munich: 1969, pp. 727–743.
21. Sutherland, D. E. R., Matas, A. J., Steffes, M. W. and Najarian, J. S.: Infant Human Pancreas: A Potential Source of Islet Tissue for Transplantation. Diabetes, 25:1123, 1976.
22. Sutherland, D. E. R., Steffes, M. W., Bauer, G. E., et al.: Isolation of Human and Porcine Islets of Langerhans and Islet Transplantation in Pigs. J. Surg. Res., 16:102, 1974.
23. Ziegler, M. M., Reckard, C. R., Naji, A., and Barker, C. F.: Extended Function of Isolated Pancreatic Islet Isografts and Allografts. Transpl. Proc., 7:743, 1975.

New (5th) Edition!

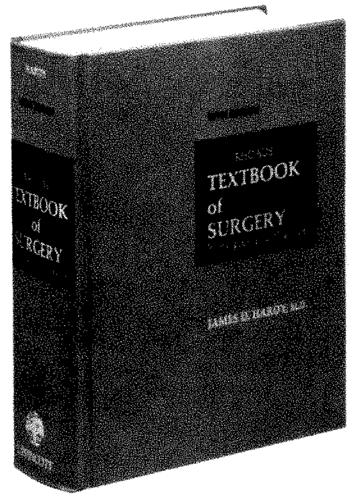


Rhoads
TEXTBOOK OF SURGERY
Principles and Practice

Edited by

JAMES D. HARDY, M.D.

With 279 contributors.



Now Available in Either One or Two Volume Form!

New Features:
- Content
- Approach
- Editor
- Format
- Contributors

Although technically a New (5th) Edition of *Surgery: Principles and Practice*, this revision is new in *title, editor, contributing authors, content, approach, and format.* It has been reorganized into three major parts: General Principles of Surgical Practice; Specific Lesions and Dysfunctions Involving Various Organs; and Parasurgical Considerations.

The approach is now problem-oriented and this outstanding volume considers virtually all current problems in surgery.

More than 270 contributors give you an enormous geographical and philosophical range in one volume. Each is well known in his field and discusses management of a specific problem. Included in each of the hundreds of topics discussed are basic features of the operation including a table of basic facts; an overview of the concept under discussion; description of specific pathological conditions; surgical history; physiology; a pathophysiological diagram and an anatomical sketch whenever feasible; many excellent illustrations of disease processes and treatment procedures; possible technical errors; safeguards; postoperative problems; and complications.

2354 Pages / 1738 Illustrations / 313 Tables
5th Edition, 1977 / One Volume Format: $38.50
Two Volume Format: $45.00

Lippincott

J. B. Lippincott Company ● East Washington Square ● Philadelphia, Pa. 19105

In Canada: J. B. Lippincott Company of Canada Ltd. ● 75 Horner Avenue ● Toronto, Ontario M8Z 4X7

Please send me:

HARDY, Rhoads TEXTBOOK OF SURGERY, 5th Edition ....☐ **1-vol., $38.50**
☐ **2-vols., $45.00**

Name ______________________ Address ______________________

City ______________________ State ______________________ Zip __________

☐ Payment enclosed (save postage & handling) ☐ Charge & bill me (plus postage & handling)

Also available at your medical bookstore AS 1/78

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

Adria Laboratories Inc.
  Adriamycin 30A,31A

Amersham Corp.
  Ibrin 36A,37A,38A

Beecham Laboratories
  Tigan 54A,55A

Boehringer Ingleheim Ltd.
  Dulcolax 11A

Bristol Laboratories
  Kantrex 56A,57A
  Prostaphlin 43A

Burroughs Wellcome Company
  Empirin Compound w/Codeine #3/Empracet w/Codeine #3 Cover IV

Eaton Laboratories
  Vivonex 8A,9A

Endo Inc.
  Percocet 46A,47A

Knoll Pharmaceuticals
  Dilaudid Cover II

Lederle Laboratories
  Amicar 12A,13A,14A

Eli Lilly & Company
  Keflin 34A,35A

Parke, Davis & Company
  Chloromycetin 4A,5A,6A

Pfizer Laboratories Division
  Vistaril 52A,53A,54A

Roche Laboratories
  CEA 28A,29A

Searle Laboratories
  Metamucil 15A

Smith Kline & Frech Labs.
  Ancef 48A thru 50A
  Compazine 58A. Cover III

Upjohn Pharmaceutical
  Cleocin Phosphate 20A thru 23A

Winthrop Laboratories
  Talwin Oral 24A thru 26A

SUPPLIES & EQUIPMENT

Affiliated Hospital Products Inc.
  A X 8 Surgical Light 51A

Rudolph Beaver Inc.
  Mini-Blades 1A

Davis & Geck
  Surgilene Sutures Direct Dispensing Packages 39A,40A

Dome Laboratories
  Paste Bandage 33A

Ethicon Inc.
  Ethibond Sutures 44A,45A,46A

Life Sciences Inc.
  Pulse Volume Recorder 16A

Olympus Corporation of America
  GIF-D3 Standard Fiberscope 19A

Purdue Frederick Company
  Betadine Surgical 3A

MISCELLANEOUS

King Faisal University 14A,32A

J. B. Lippincott Company 15A,17A,27A,38A,41A

New York University 32A

Xerox University Microfilm 32A

Every day, healthy people leave the hospital–carrying resistant staph.

Today, more than 80%* of community staph is resistant to penicillin G.

Treat these resistant staph infections as effectively in the office as you do in the hospital.

Prostaphlin®
(oxacillin sodium)

*Ross, S. *et al.*: JAMA *229*:1075 (Aug. 19) 1974.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Prostaphlin® (oxacillin sodium)
Capsule and Oral Solution (11) PROSTAPHLIN 9/11/75

For complete information, consult Official Package Circular.

Indications: Although the principal indication for oxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to oxacillin sodium should be performed.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of oxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to oxacillin sodium, the physician is advised to continue therapy with a drug other than oxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Oxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A previous hypersensitivity reaction to any penicillin is a contraindication.

Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

The possibility of bacterial and/or fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Experience in premature and newborn infants is limited. Caution should be exercised in administration of the drug to such patients and frequent evaluation of organ system function is recommended.

Safety for use in pregnancy has not been established.

Adverse Reactions: The hypersensitivity reactions reported are skin rashes, urticaria, serum sickness and anaphylactic reactions. Oral lesions such as glossitis and stomatitis have been reported. Fever, eosinophilia, oral and rectal moniliasis have also been reported. Hemolytic anemia, transient neutropenia with evidence of granulocytopenia or thrombocytopenia, neuropathy, and nephrotoxicity (oliguria, albuminuria, hematuria, pyuria, and/or cylindruria) are infrequent and usually associated with high doses of parenteral penicillin.

In some newborns and infants receiving high doses of oxacillin sodium (150 to 175 mg./Kg./day), transient hematuria, albuminuria, and azotemia have been encountered. Although the causal relationship is not entirely clear, infants and newborns treated with high doses of the drug should be observed closely for signs of renal impairment.

One patient developed granulocytopenia while receiving intravenous oxacillin sodium and vancomycin. The blood count returned to normal after both drugs were discontinued. Another patient was reported to have leukopenia during intravenous therapy with oxacillin sodium. These counts were made while the patient was moribund. Thrombophlebitis has occurred in a small percentage of patients after intravenous therapy.

Usual Oral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Administer on empty stomach for maximum absorption.

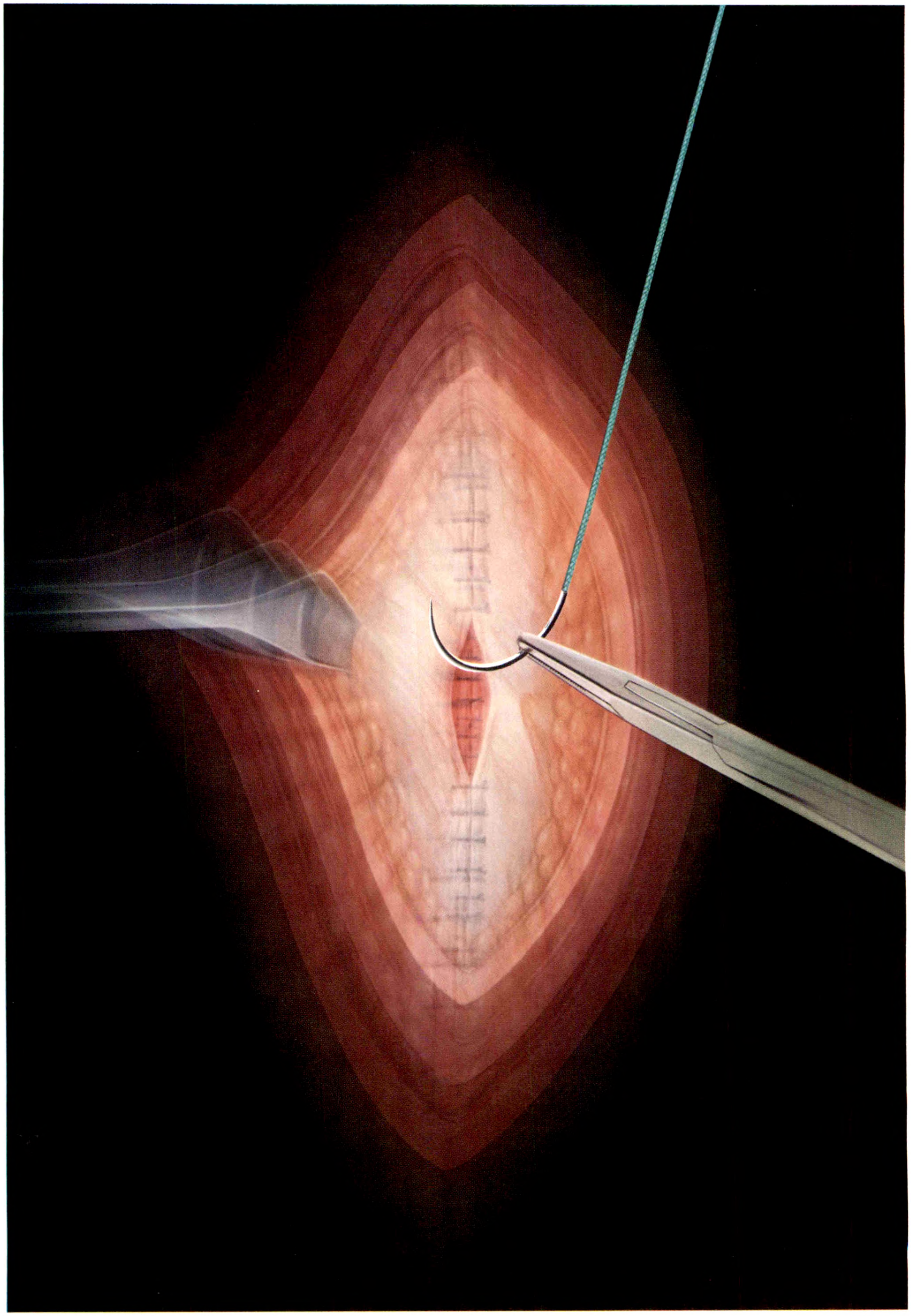
Usual Parenteral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Children weighing 40 Kg. or more should receive the adult dose.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

Supplied: Capsules—250 and 500 mg. in bottles of 48 and 100. Injectable—250 mg., 500 mg., 1 Gm., 2 Gm., and 4 Gm. dry filled vials for IM/IV use. For Oral Solution —100 ml. bottles, 250 mg./5 ml. when reconstituted.

A.H.F.S. Category 8:12.16

BRISTOL®
BRISTOL LABORATORIES
Division of Bristol-Myers Co.



Only

ETHIBOND*

POLYESTER SUTURE

has polybutilate

...the first coating designed for surgery

All coated sutures available until now have been coated with commercial lubricants. ETHIBOND suture, a braided polyester, is coated with polybutilate, also a polyester but developed specifically for surgical use.

Since polyester coating has a natural affinity for polyester braid, a strong cohesive attraction forms — and minimum polybutilate is required for maximum lubrication. Each suture is uniformly coated according to size, virtually eliminating any possibility of the lubricant's flaking, shredding or beading. Thus, ETHIBOND suture exhibits less tissue reaction compared to sutures which tend to exfoliate their coating.

With its minimum polybutilate coating, ETHIBOND suture has a soft, pliable hand — easy to tie and knot. It passes through tissue with an ease that can be compared to monofilament suture materials. It has high tensile strength, and retains its strength in vivo.

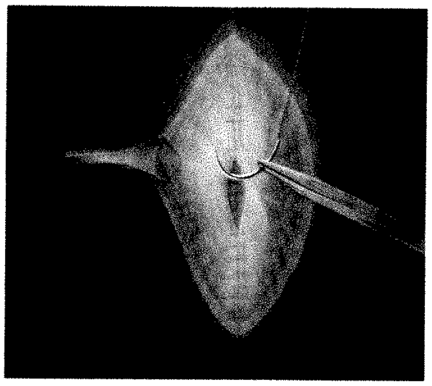
ETHIBOND suture is available in a full range of sizes, in precut unthreaded sutures or swaged to Super-Smooth needles specifically designed for general surgery.

The general surgeon will find ETHIBOND suture an excellent choice for skin closure, fascial closure, hernia repair and GI anastomosis, affording ease of passage through tissue, minimal reactivity and patient comfort during suture removal.

ETHICON

*Trademark (See next page for complete product information.) © ETHICON, INC. 1976

COMPLETE PRODUCT INFORMATION



ETHIBOND*

POLYESTER SUTURE NONABSORBABLE SURGICAL SUTURE, U.S.P.

DESCRIPTION

ETHIBOND suture is nonabsorbable, braided, polyester (polyethylene terephthalate or MERSILENE* polyester) fiber uniformly coated with polybutilate, or poly [oxy-1, 4-butanediyloxy (1,6-dioxo-1,6-hexanediyl)]. The highly adherent coating is a biologically inert, nonabsorbable compound which acts as a lubricant to mechanically improve the physical properties of the uncoated suture by improving ease of passage through tissues and by providing overall improved handling qualities as contrasted to the braided, uncoated fiber.

ETHIBOND sutures are sterile, inert, and elicit minimal tissue reaction. They are braided for optimal handling properties, and for good visibility in the surgical field the dyed sutures are colored with D&C Green No. 6.

ACTIONS

ETHIBOND sutures are strong, nonabsorbable sutures: subcutaneous tissue implantation in rats shows that no significant change in the retention of tensile strength of the suture occurs during the entire evaluation period of 180 days. Both the polyester fiber suture material and the polybutilate coating are pharmacologically inactive.

INDICATIONS

ETHIBOND suture is intended for use as a nonabsorbable suture.

CONTRAINDICATIONS

None

WARNINGS

ETHIBOND polyester sutures have not been evaluated in ophthalmic surgery.

Do not resterilize.

PRECAUTIONS

As with all sutures, acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

Knot security requires the standard surgical technique of flat and square ties, with additional throws if indicated by surgical circumstance and the experience of the operator.

Two-year carcinogenicity studies in Long-Evans rats demonstrated no carcinogenic potential.

ADVERSE REACTIONS

Slight erythema and/or induration at suture sites have been reported in approximately 2% of the patients in whom ETHIBOND sutures have been used, a not unexpected reaction.

DOSAGE AND ADMINISTRATION

Use as required per operation.

HOW SUPPLIED

ETHIBOND sutures are available sterile as green braided and undyed (white) strands in sizes 5 to 7/0 in a variety of lengths, with and without needles, in one and three dozen units.

*Trademark

ETHICON

Tablets

Percocet®-5 Ⓒ II

DESCRIPTION Each tablet of PERCOCET®-5 contains 5mg oxycodone hydrochloride (WARNING: May be habit forming), 325mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories, Inc
Subsidiary of the DuPont Company

DUPONT
REG. U.S. PAT. & TM. OFF.

November 1977 EDO 148P

FOR MODERATE TO MODERATELY SEVERE PAIN

Acetaminophen with the narcotic difference

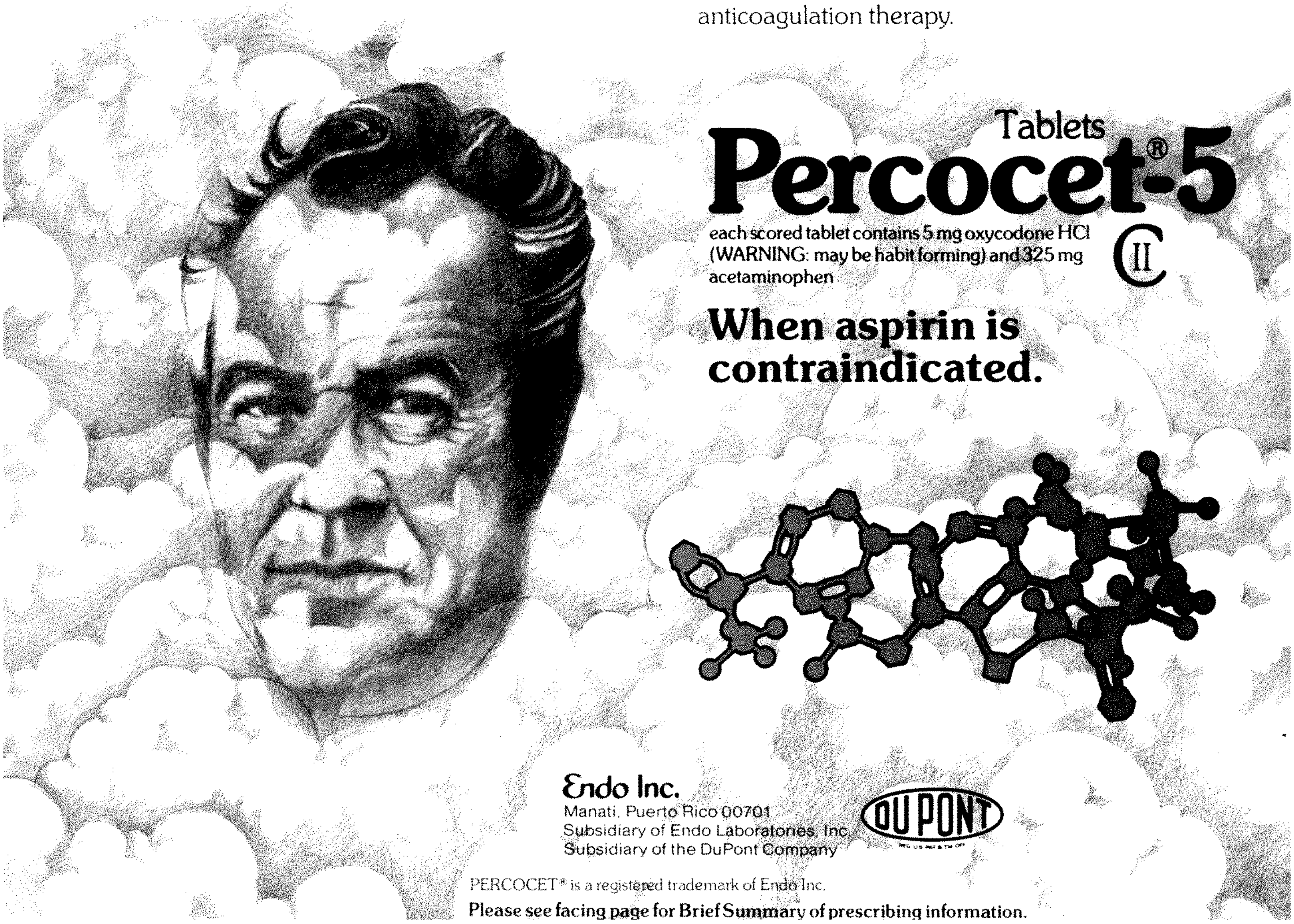
Reliable oral narcotic analgesia...

The narcotic component in PERCOCET®-5 is oxycodone, which is readily absorbed and provides dependable oral analgesia — usually within 15 to 30 minutes. Oxycodone can produce drug dependence of the morphine type and should be prescribed with the same degree of caution appropriate to the use of other narcotic-containing medications.

...aspirin free

Acetaminophen is a non-narcotic analgesic widely used for aspirin-sensitive patients. Equivalent to aspirin in analgesia, it complements the pain relief provided by oxycodone.

The usual dose of PERCOCET®-5 is one tablet every six hours, providing convenience and economy for your patients. PERCOCET®-5 is ideally suited for your patients with aspirin sensitivity, with hemostatic disturbance, with peptic ulcer or on anticoagulation therapy.



Tablets

Percocet®-5

each scored tablet contains 5 mg oxycodone HCl (WARNING: may be habit forming) and 325 mg acetaminophen

Ⓒ II

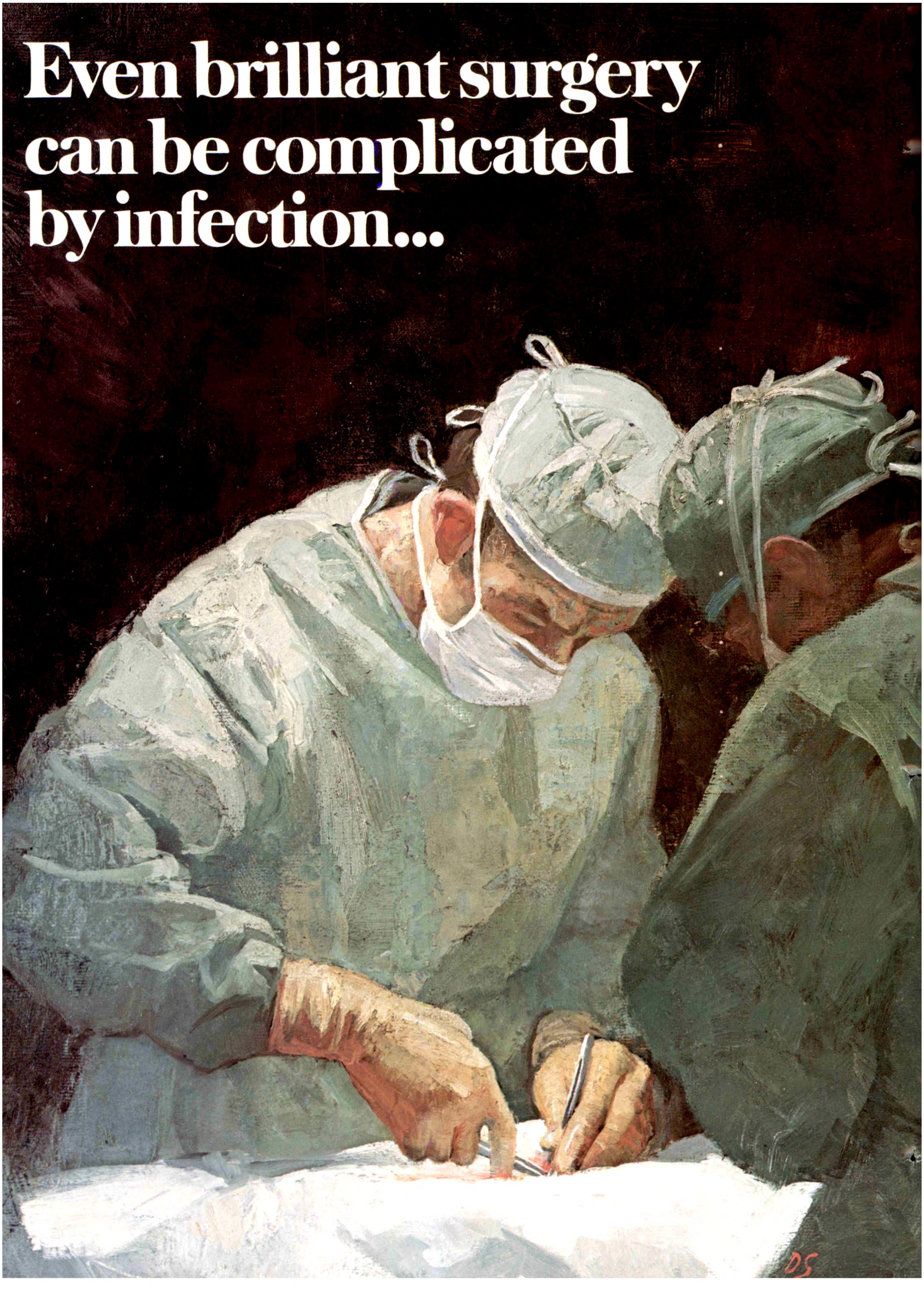
When aspirin is contraindicated.

Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories, Inc.
Subsidiary of the DuPont Company

DU PONT

PERCOCET® is a registered trademark of Endo Inc.

Please see facing page for Brief Summary of prescribing information.


Even brilliant surgery can be complicated by infection...
DS

ANCEF® is effective in post-surgical infections*

- *Broad coverage of the major areas of post-surgical infection due to susceptible organisms. See Indications on next page.

- High Levels Present in Tissues and Fluids†
Ancef® achieves high concentrations in bone, synovial fluid, skin and soft tissues (such as pleural fluid, peritoneal fluid and lymph nodes). Ancef® is also excreted in a microbiologically active form in urine.

- High and Prolonged Serum Levels
A single 1 gram IV injection produced a mean peak concentration of Ancef® of 190 mcg/ml in healthy adult volunteers. After 4 hours, levels of 16.5 mcg/ml were still present.

- IM or IV Dosage Flexibility
The same dosage schedule can be used for both IM and IV administration.

- Well Tolerated
Most frequently reported adverse reaction is pain on injection. Please see next page for a complete list of reported adverse reactions. **Use with caution in patients with penicillin or other allergies.**

Please see next page for a brief summary of prescribing information, including indications, contraindications, warnings, precautions, and adverse reactions.

†Data on file, SK&F Medical Department. Tissue penetration is regarded as essential to therapeutic efficacy, but specific antibiotic tissue levels have not been directly correlated with specific therapeutic effects.

Smith Kline &French Laboratories
Philadelphia, Pa.

ANCEF® IV IM
brand of sterile
CEFAZOLIN SODIUM
(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

SK&F
a SmithKline company

ANCEF® IV/IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

Most infections can be treated with 500 mg. or 1 gram of 'Ancef' every 8 hours.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Ancef® (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms.

Respiratory tract infections due to *Streptococcus (Diplococcus) pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus.*

Septicemia due to *Str. pneumoniae, S. aureus* (penicillin-sensitive and penicillin-resistant), *P. mirabilis, E. coli,* and *Klebsiella* species.

Endocarditis due to *S. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

Contraindications: 'Ancef' is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Antibiotics, including 'Ancef', should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infants—Safety for use in prematures and infants under one month of age has not been established.

Precautions: Prolonged use of 'Ancef' may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to adults or children with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions in the package literature).

A false-positive reaction for glucose in the urine may occur with Clinitest® tablets; use glucose enzyme-type reagents.

Adverse Reactions: The following reactions have been reported: Drug fever, skin rash, vulvar pruritus, eosinophilia, neutropenia, leukopenia, thrombocythemia, and positive direct and indirect Coombs tests have occurred. Transient rise in SGOT, SGPT, BUN, and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment. Nausea, anorexia, vomiting, diarrhea, and oral candidiasis (oral thrush) have been reported. Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

Administration and Dosage: 'Ancef' may be administered intramuscularly or intravenously after reconstitution. See the package literature for reconstitution procedures.

See the package literature for dosage recommendations.

How Supplied: 'Ancef' (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg. or 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 500 mg. or 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

Smith Kline &French Laboratories
Philadelphia, Pa.

SK&F
a SmithKline company

Human Parathyroid Cryopreservation:

In Vitro *Testing of Function by Parathyroid Hormone Release*

MURRAY F. BRENNAN, M.D., EDWARD M. BROWN, M.D., HENRY F. SEARS, M.D.,
GERALD D. AURBACH, M.D.

The functional viability of cryopreserved human parathyroid tissue was assessed by determining suppressibility of parathyroid hormone release by evaluation of ambient calcium concentration. Parathyroid hormone release from dispersed human parathyroid cells prepared from both fresh tissue and tissue cryopreserved for up to 200 days was suppressed 0–90% in response to four-fold increases in calcium concentration. In the tissue that demonstrated suppression precryopreservation, the suppression curve was similar in form postcryopreservation. The ability to retain functional integrity within human parathyroid cells by cryopreservation, allows preservation for periods of time probably sufficient to determine the presence of the aparathyroid state, and allows for subsequent successful parathyroid autotransplantation. This technique has particular applicability to patients reoperated upon for persistent hyperparathyroidism where the remaining amount of normal parathyroid tissue is obscure or unknown.

From the Surgery Branch, National Cancer Institute and Metabolic Diseases Branch, National Institute of Arthritis and Metabolic Disease, National Institutes of Health, Bethesda, Maryland

CRYOPRESERVATION OF HUMAN parathyroid tissue would be a useful adjunct to autotransplantation of parathyroid tissue into the human forearm[3,7,15] an approach which has recently been shown to be potentially useful in the management of patients with primary and secondary hyperparathyroidism.[3,15,16] In patients having undergone previous unsuccessful surgery for hyperparathyroidism, the amount of residual normal or abnormal parathyroid tissue is frequently uncertain, and the chance of successful reoperation leaving the patient hypoparathyroid is significant. This assessment is difficult even with review of previous operative notes and histological specimens. It is sometimes difficult to determine the exact completeness of gland removal and a small percentage of patients have five or even six glands.[13] Parathyroid tissue maintained cryopreserved following definitive surgery would constitute a tissue bank for subsequent autotransplantation if permanent hypoparathyroidism develops. This is a particular problem for this department where in the last 18 months 25 patients have been operated on for persistent hyperparathyroidism following a total of 53 prior operative procedures.

We have been concerned, however, that cryopreservation might damage the tissue in such a manner as to make it unsuitable for autotransplantation. In attempting to determine the viability and function of cryopreserved tissue we have compared the function of parathyroid cells prepared from tissue immediately after removal at surgery with that of the same cells at intervals after cryopreservation. We have previously shown that dispersed cells prepared from either bovine[4] or human parathyroid tissue[5] are viable by a variety of morphologic and functional criteria. The present studies show that tissue frozen for up to seven months is functional and suggest the utility of this method for predicting the viability of cryopreserved tissue *in vivo*.

Materials and Methods

In the period 8/15/75–8/15/76 human parathyroid tissue was cryopreserved from surgical specimens obtained from 19 patients. Thirteen of these patients had undergone prior parathyroid surgery but remained hypercalcemic. In six of this latter group there was a high probability that the contemplated definitive surgery would render them aparathyroid. The cryopreservation technique involved removal of the specimen, surgical debridement of all extraneous fibro-fatty tissue and the sharp division of the gland into small tissue slivers approximately 2 × 1 × 3 mm. These were

---

Reprint requests: Surgery Branch, National Cancer Institute, Building 10, Room 10N116, Bethesda, Maryland 20014.

Submitted for publication: April 11, 1977.

0003-4932-78-0100-0087-0060 © J.B. Lippincott Company

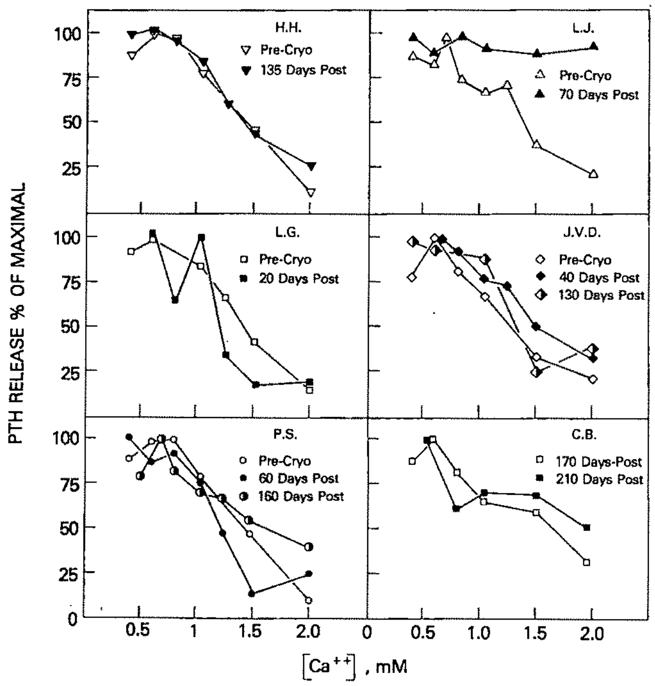


FIG. 1. Pre- and Postcryopreservation suppression curves for five patients with parathyroid adenomas and one with primary parathyroid hyperplasia (C.B.). 400,000–800,000 dispersed parathyroid cells/ml were incubated in standard medium with 0.2% bovine serum albumin, 0.5 mM $MgSO_4$ calcium for two hours at 37°. Samples were assayed for PTH as described in methods. Results are expressed as per cent of maximal PTH released at low calcium.

placed immediately in iced saline and removed in a sterile manner from the operating room. Six to eight fragments each of the tissue to be cryopreserved were placed in polypropylene vials and to this was added 0.5cc 20% human autologous serum in RPMI 1640 media to which fresh glutamine and penicillin-streptomycin had been added; 0.5cc's of a 20% Dimethylsulfoxide (DMSO) solution (made by adding 1cc absolute DMSO to 4cc of the RPMI glutamine pen-strep solution) was added just prior to placing the vials in the freezing unit (programmed to remove heat at a rate of 1–2°C/min.).[*] Following cryopreservation, the vials are removed and placed immediately in the vapour phase of a liquid nitrogen freezer at −170°. The thawing procedure involved removing the tissue vial and placing it immediately in a 42° waterbath. The vials are gently moved in the waterbath until the ice crystal has almost completely melted. The tissue is then removed and kept at room temperature and RPMI glutamine pen-strep (see above) is added drop-wise in 100 microliter increments to a total added volume of 500 microliters. After five minutes, a further 500 microliters of the same solution is added. Following a further ten minutes, 1.5cc's of the total supernatant is then removed with a 1cc pipette and the RPMI solution once again added in 1cc increments for a total of 3cc, removing 1cc prior to each new addition.

Dispersed parathyroid cells were prepared as described previously.[4] In brief, immediately upon surgical removal or immediately following thawing, the tissue was placed in cold (4°) Eagle's medium number 2 (bicarbonate deleted) with 0.02 M Hepes pH 7.47 ("standard medium") 0.5 mM $CaCl_2$ and $MgSO_4$, 0.2% collagenase (Worthington type 1 or 3) and DNase 50 micrograms/ml.[†] The turbid solution was filtered through nylon mesh and washed two to three times with standard medium containing two per cent albumin, 1.5 mM $CaCl_2$ and 0.5 mM $MgSO_4$ by repeated sedimentation and resuspension. Incubations were carried out in 20 ml plastic scintillation vials in a shaking incubator at 37° in standard medium with 0.2% albumin and variable calcium (0.5 to 2.0 mM) and magnesium concentrations. Viability as assessed by trypan blue exclusion was routinely 95–100%, except where indicated.

Samples were removed, frozen for subsequent radioimmunoassay for parathyroid hormone as described previously[4] using a guinea pig antibovine parathyroid hormone antibody (GP-4). Results are expressed as ng/ml of human PTH, using highly purified human parathyroid hormone as a standard.

Results

Parathyroid cells of 8 patients tested before cryopreservation released detectable parathyroid hormone *in vitro*. Six showed clear evidence of a 60% or greater suppression of release with elevation of calcium concentration (Table 1). Cells from two showed no suppression of PTH release; both had large cystic glands which contained many cells that appeared necrotic.

The suppressibility of PTH release by isolated cells prepared from parathyroid tissue cryopreserved for varying periods of time is also shown in Table 1. Cells from five parathyroid adenomas showed similar suppressibility of PTH release before as well as after cryopreservation for varying periods. The degree of suppressibility as per cent of maximal secretion as well as apparent ½-maximal effect of calcium were very similar before or after cryopreservation (Fig. 1). Maximal PTH release per 100,000 cells, however, was decreased by 10–60% following freezing, although there was no consistent relationship to the period of

---

[*] Planar Products programmed freezer %201, Sunbury on Thames, Middlesex, England.

[†] Sigma DNase-IIH.

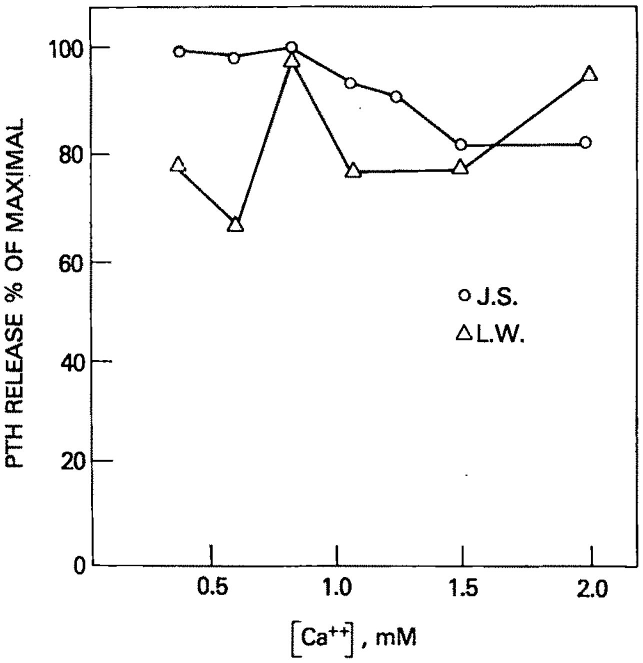


FIG. 2. Precryopreservation curves for two patients in whom suppression was not observed either pre- or postcryopreservation. Cell incubations and PTH determinations carried out as in Methods.

cryopreservation. Tissue from R.B. responded prior to cryopreservation, but cell yield upon thawing was too poor to allow testing over a full range of calcium concentrations. Hormone release at high calcium (2.0 mM) was 40% of that at low calcium (0.5 mM) at 45 days of storage, suggesting functional integrity of the cells. In one instance (material from L.J.) cryopreserved cells showed no suppression in several experiments even though PTH released was abundant and the same cells had responded to calcium before freezing. In two instances (tissue from J.S. and L.W.) there was no response to calcium either before or after freezing. In both, cell yield was poor and trypan blue exclusion lower than usual (50–70% vs 95–100%) (Fig. 2).

Tissue from one patient (C.B.) not tested before freezing was tested at 170 days, then refrozen and retested at 210 days (Fig. 1). Secretion was suppressible at each time. This patient has recently undergone autotransplantation with this tissue but function has not yet been evaluated *in vivo*.

Discussion

Human blood cell elements[1,6,8,9,11,12] are readily stored frozen for future use and upon thawing routinely show virtually complete viability and function. Morphologic evidence of successful freezing of parathyroid glands was presented in 1950.[2] Functional recovery of parathyroid secretion using frozen stored parathyroid glands has since been documented in the rat.[10,14] Rat parathyroid glands cryopreserved for three to nine months become fully functional upon transplantation into parathyroidectomized syngeneic hosts.[14] At 12 months, however, results of the latter study were less encouraging. Clearly, assessment of viability would be imperative for clinical transplantation studies. *In vivo* testing, however, is time-consuming and not feasible with human tissue. A simple, rapid test of functional viability would, therefore, be desirable to predict potential graft viability. The dispersed cell system recently described for human or bovine parathyroid tissue should provide a means to test for function and physiologic response to calcium. Indeed, the present results suggest that suppressibility of PTH release by cryopreserved tissue might be a relatively simple and rapid index of functional integrity before reimplantation. The test appears to be valid for either hyperplastic or adenomatous parathyroid tissue, although the apparent one-half maximal effective concentration of calcium may differ between cells from two types of tissue.[5] This test would not, of course, assess the replicative capacity of the tissue and ultimately must be correlated with the survival of tissue posttransplantation. Survival has been documented by successful *in vivo* transplantation of an adenomatous gland after 12 weeks of storage,[3] and of a

TABLE 1

	Precryopreservation		Postcryopreservation	
Patient	Pathology	Suppressibility	Days Stored	Suppressibility
L.G.	Ad	†	20	†
J.V.D.	Ad	†	40 160	† †
P.S.	Ad	†	60 160	† †
L.J.	Ad	†	70 115	— —
H.H.	Ad	†	135	†
J.S.	Ad	—	70	—
R.B.	Hyp	†	18 21 45	—* —* †
L.W.	Hyp	—	25 30	—* —*
C.B.	Hyp	‡	170 210	† †

* Insufficient Cells Hyp = hyperplasia Ad = Adenoma
Suppressibility, † = at least 60% decrease in maximal PTH release with increase in calcium concentration.
‡ = Test not performed.

hyperplastic gland after six weeks of freezing.[17] The present study continues with *in vivo* correlation with the *in vitro* assay, and further assessment of optimal cryopreservation techniques.

References

1. Bender, M. A., Tran, P. T and Smith, L. H.: Preservation of Viable Bone Marrow Cells by Freezing. J. Appl. Physiol., 15:520, 1960.
2. Blumenthal, H. T. and Walsh, L. B.: Survival of Guinea Pig Thyroid and Parathyroid Autotransplants Previously Subjected to Extremely Low Temperatures. Proc. Soc. Exp. Biol. Med., 73:62, 1950.
3. Brennan, M. F., Marx, S. J., Brown, E. M., et al.: Management of Primary Parathyroid Hyperplasia. N. Engl. J. Med., 295:1202, 1976.
4. Brown, E. M., Hurwitz, S. and Aurbach, G. D.: Preparation of Viable Isolated Bovine Parathyroid Cells. Endocrinology, 99:1582, 1976.
5. Brown, E. M., Brennan, M. F., Hurwitz, S. and Aurbach, G. D.: (unpublished observations).
6. Handin, R. I. and Valeri, C. R.: Improved Viability of Previously Frozen Platelets. Blood, 40:509, 1972.
7. Hickey, R. C. and Samaan, N. A.: Human Parathyroid Autotransplantation. Arch. Surg., 110:892, 1975.
8. Kim, B. K. and Baldini, M. G.: Preservation of Viable Human Platelets by Freezing. Blood, 40:939, 1972.
9. Kim, B. K., and Baldini, M. G.: Biochemistry, Function and Hemostatic Effectiveness of Frozen Human Platelets. Proc. Soc. Exp. Biol. Med., 145:830, 1974.
10. Russell, P. S., Wood, M. L. and Gittes, R. F.: Preservation of Living Tissue in the Frozen State. A Study Using Parathyroid Tissue. J. Surg. Res., 1:23, 1967.
11. Sears, H. F. and Rosenberg, S. A.: Advantages of Cryopreserved Lymphocytes for Sequential Evaluation of Human Immune Competence. I. Mitogen Stimulation. J. Natl. Cancer Inst., 58:183, 1977.
12. Strong, D. M., Woody, J. N., Factor, M. A., et al.: Immunological Responsiveness of Frozen-Thawed Human Lymphocytes. Clin. Exp. Immunol., 21:442, 1975.
13. Wang, C. A.: The Anatomic Basis of Parathyroid Surgery. Ann. Surg., 185:271, 1976.
14. Wells, S. A. and Christiansen, C.: The Transplanted Parathyroid: Evaluation of Cryopreservation and Other Environmental Factors which Affect its Function. Surgery, 75:49, 1974.
15. Wells, S. A., Gunnells, J. C., Shelburne, J. D., et al.: Transplantation of the Parathyroid Glands in Man: Clinical Indications and Results. Surgery, 78:34, 1975.
16. Wells, S. A., Ellis, G. J., Gunnells, J. C., et al.: Parathyroid Autotransplantation in Primary Parathyroid Hyperplasia. N. Engl. J. Med., 295:57, 1976.
17. Wells, S. A., Gunnells, J. C., Gutman, R. A., et al.: The Successful Transplantation of Frozen Parathyroid Tissue in Man. Surgery, 1:81, 1977.

Control of Gastric Emptying:

Interaction of the Vagus and Pyloric Antrum

T. YAMAGISHI, M.D., H. T. DEBAS, M.D.

From the Department of Surgery, University of British Columbia, Vancouver, B.C., Canada

Gastric emptying of liquids and solids was evaluated in ten dogs with gastric fistula before and after either truncal vagotomy, antrectomy, or pyloroplasty. In subsequent operations, the vagotomy group underwent either antrectomy or pyloroplasty, and the antrectomy and pyloroplasty groups were vagotomized. Vagotomy significantly inhibited the emptying of both liquids and solids ($p < 0.001$) when the pyloric antrum was intact. When the antropyloric mechanism was removed by antrectomy, the effect of vagotomy was to accelerate the emptying of liquids ($p < 0.05$) but to impair the emptying of solids ($p < 0.001$). When the pylorus was destroyed by pyloroplasty, vagotomy markedly accelerated the emptying of liquids but had little effect on the emptying of solids. Neither antrectomy nor pyloroplasty had any significant effect on the emptying of solids. Pyloroplasty caused minor acceleration of emptying of liquids while antrectomy had no effect.

IT HAS BEEN SUGGESTED that the proximal stomach controls the emptying predominantly of liquids and that the emptying of solids is primarily regulated by the distal stomach.[10] In this concept any role the pylorus might play is not stressed. At least in part, the trend to minimize the role of the pylorus arises from several reports that have shown that the destruction of the pylorus either by pyloroplasty or by resection does not affect the emptying rate of liquids and solids.[2,5] Many reports that purport to describe changes that occur after vagotomy in fact discuss changes after vagotomy and drainage.

The aim of this study was to investigate the interaction of the vagus and the pylorus in the control of gastric emptying. We attempted to overcome three defects of many previous studies as follows: 1) in our studies each animal served as its own control; 2) we used as the test meal for solids ordinary food rather than solid spheres; and 3) we randomized the operations to allow us to study the effect of vagotomy after pyloroplasty or antrectomy, and the effect of pyloroplasty and antrectomy after vagotomy.

Methods

Operative Procedures

In each of ten dogs a wide bore Thomas cannula was inserted in the most dependent portion of the body of the stomach to serve as a gastric fistula (GF). This cannula facilitated the determination of the rate of gastric emptying by providing access to the stomach to enable its complete evacuation. After control studies of the rate of emptying of liquids and solids, the dogs were randomly divided into three groups: a group of three underwent antrectomy with gastroduodenal anastomosis; in the second group (two dogs) a Heineke-Mikulicz pyloroplasty was fashioned; and in the last group (five dogs) transthoracic truncal vagotomy was performed. Following recovery from these operations, all the experiments of the first stage were repeated. The dogs then underwent a final operation during which the antrectomy and pyloroplasty groups underwent transthoracic vagotomy, and the vagotomy group underwent either antrectomy (three dogs) or pyloroplasty (two dogs). After the last operation, therefore, six dogs with vagotomy and antrectomy and four with vagotomy and pyloroplasty were available for study. Again all the experiments of the first and second stages were repeated. After each operation, a recovery period of three weeks was allowed before

---

Correspondence: H. T. Debas, M.D., Department of Surgery, U.B.C., 700 West 10th Avenue, Vancouver, B.C. V5Z 1L5, Canada.

Supported by grants from the National Institute of Arthritis, Metabolism, and Digestive Diseases (1ROI AM18508-0) and the Medical Research Council of Canada (MA-5428). Dr. Yamagishi holds a fellowship grant from the British Columbia Medical Services Foundation.

A preliminary report appeared in abstract form (Gastroenterology 70:952, 1976).

Submitted for publication: April 21, 1977.

0003-4932-78-0100-0091-0060 © J.B. Lippincott Company

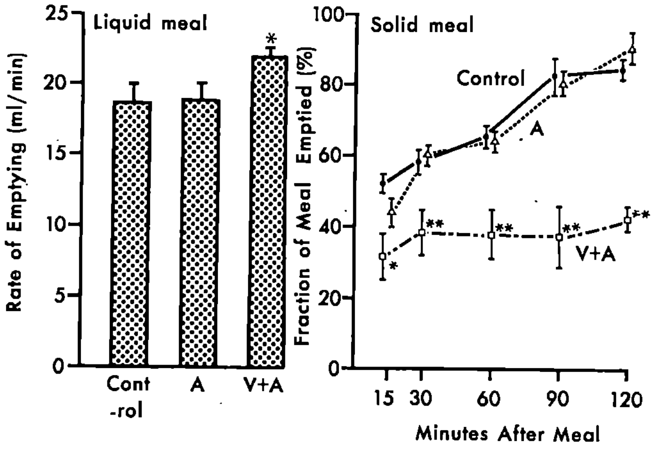


FIG. 1. (Left Panel) Mean ± SE rate of emptying of a liquid meal in three dogs preoperatively (control), following antrectomy alone (A), and following subsequent truncal vagotomy (V&A). (Right Panel) Mean ± SE fraction of a solid meal emptied during the three stages: control, antrectomy, and truncal vagotomy and antrectomy. In this and subsequent figures each bar represents mean of at least five experiments in each dog, and each point in the right panel represents mean of two experiments on each dog. Asterisks represent significance of the difference from control; one asterisk indicates $p < 0.05$, two asterisks $p < 0.001$.

testing commenced. Each stage lasted about three months.

Determination of Rate of Gastric Emptying of Liquid Meal

The rate of gastric emptying was determined by measuring the volume of fluid remaining in the stomach ten minutes after instillation via gastric fistula of 300 ml of 0.15 M NaCl containing phenol red (60 mg/L) as indicator. The concentration of phenol red was determined in both the meal instilled and the fluid drained from the stomach at the end of the ten minute period. Samples of 1.0 ml and 2.0 ml of a solution of Na_3PO_4 (27.5 g/L) were pipetted into a 10 ml volumetric flask which was then filled to the mark with distilled water. After thorough mixing the optical density of the solution was read at 550 nm against water blank in a Coleman Junior spectrophotometer. Rate of gastric emptying was calculated from the formula:

$$\text{Rate of emptying (ml/10 minutes)} = \frac{(ViPi) - (VrPr)}{(Pi + Pr)/2}$$

where Vi and Vr = volume of fluid instilled and recovered respectively,
Pi and Pr = concentration of phenol red in fluid instilled and recovered respectively.

The assumption is made that the concentration of phenol red in fluid leaving the stomach is the mean of the initial and final concentrations.

Determination of Rate of Emptying of Solid Meal

The solid meal consisted of proprietory dog food (Dr. Ballard's, Canada) equivalent in dry weight to 3 g/kg body weight. The dogs were fasted for at least 18 hours, and the gastric fistula opened and the stomach rinsed gently with water. The gastric fistula was then corked, and the dogs allowed to eat the meal. The gastric fistula was again opened either at 15, 30, 60, 90, or 120 minutes after the completion of the meal and the residual food emptied. The stomach was rinsed with copious amounts of water to ensure complete recovery of the entire residual meal. This was then dessicated and weighed. The difference in dry weight between the meal ingested and the food recovered from the stomach represents the amount of solid food that left the stomach during the interval between ingestion of the meal and evacuation of the gastric residue. This procedure proved to be remarkably reproducible and simpler than we anticipated. The data is expressed as the fraction (%) of the meal emptied for the given time period during which the meal was allowed to stay in the stomach.

Analysis of Results

The rate of emptying of liquids and solids was repeated at least five times in each dog in each stage. Significance of differences between the control stage and following each operation and between the operations themselves was determined by using t test for paired values.

Results

Effect of Antrectomy Alone and of Subsequent Vagotomy (Fig. 1)

In this group of three dogs in which antrectomy was the first operation, this procedure alone caused no significant change in the emptying rate of either the liquid or the solid meal. When truncal vagotomy was subsequently performed, a significant acceleration of the emptying rate of the liquid meal but a marked inhibition of the rate at which the solid meal left the stomach was observed. The fraction of solid meal emptied at 15, 30, 60, 90, or 120 minutes was significantly lower than at the corresponding times during control studies.

Effect of Pyloroplasty Alone and of Subsequent Vagotomy (Fig. 2)

Pyloroplasty alone caused a small acceleration of the rate of emptying of the liquid meal. This change was

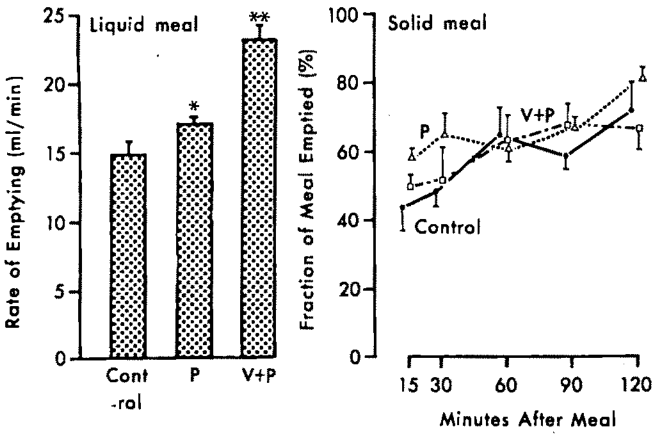


FIG. 2. (Left Panel) Mean ± SE rate of emptying of a liquid meal in two dogs preoperatively (control), following pyloroplasty alone (P), and following subsequent truncal vagotomy (V + P). (Right Panel) Mean ± SE fraction of a solid meal emptied during the three stages: control, pyloroplasty, and truncal vagotomy and pyloroplasty.

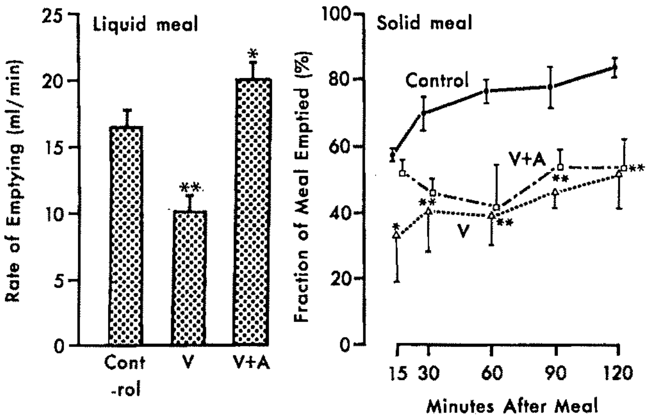


FIG. 3. (Left Panel) Mean ± SE rate of emptying of a liquid meal in three dogs preoperatively (control), following truncal vagotomy alone (V) and after subsequent antrectomy (V + A). (Right Panel) Mean ± SE fraction of a solid meal emptied during the three stages: control, truncal vagotomy alone, and vagotomy and antrectomy.

significant at the five per cent level. The emptying rate of the solid meal was, however, unaltered by pyloroplasty alone. Subsequent vagotomy caused further acceleration of the rate at which the liquid meal emptied but had no effect on the rate at which the solid meal left the stomach.

Effect of Vagotomy Alone and of Subsequent Antrectomy (Fig. 3)

Vagotomy alone markedly inhibited the rate of emptying of both the liquid and solid meals. Subsequent antrectomy produced a rate of emptying of the liquid meal that was significantly faster than control values. By contrast, antrectomy failed to improve the delayed emptying of the solid meal caused by vagotomy.

Effect of Vagotomy Alone and of Subsequent Pyloroplasty (Fig. 4)

As seen above, vagotomy caused significant inhibition of the emptying rate of both the liquid and solid meal. The addition of pyloroplasty not only corrected the delay caused by vagotomy alone but led to the marked acceleration of the rate at which the liquid meal emptied. Unlike the addition of antrectomy to vagotomy, the addition of pyloroplasty completely corrected the delay in the emptying of solids caused by vagotomy alone.

Discussion

These studies confirm the observations of Dozois, Kelly and Code[2] that removal of the antrum and pylorus leads to no major alteration in the rate at which either liquid or solid meals empty from the stomach. This implies that the proximal stomach with its innervations intact is capable of regulating the rate of gastric emptying. Addition of truncal vagotomy accelerated the rate of emptying of the liquid meal but markedly inhibited the emptying of the solid meal. An explanation for the accelerating effect of vagotomy on emptying of liquids has been provided by the elegant studies of Wilbur and Kelly[10] who suggested that, following vagotomy, the gastric fundus loses its ability of accommodation to distension, *i.e.* it loses its reservoir function. It is difficult to explain the delaying effect of vagotomy in the antrectomized group of animals on the same basis. It appears to us more likely that the explanation lies in the denervation of the small

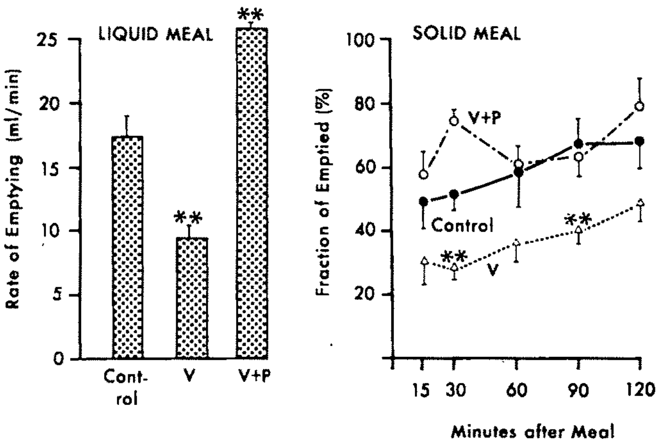


FIG. 4. (Left Panel) Mean ± SE rate of emptying of a liquid meal in two dogs preoperatively (control), following truncal vagotomy alone (V), and following subsequent pyloroplasty (V + P). (Right Panel) Mean ± SE fraction of a solid meal emptied during the three stages: control, truncal vagotomy alone, and vagotomy and pyloroplasty.

intestine that results from truncal vagotomy. This hypothesis ascribes function to the extragastric vagal branches in the control of emptying of solid meals. Gleysteen et al.[5] have recently ascribed similar importance to the hepatic and celiac vagal fibers in the control of the emptying of liquids. Whatever the mechanism (purely neural or neurohumoral), the delay of emptying of solids by truncal vagotomy in the antrectomized animal is likely the result of changes in motor action of the small intestine.

We found that pyloroplasty caused a slight acceleration of the emptying rate of liquids. Other investigators[5,7] have found that pyloroplasty was without effect. The alteration we saw is so small that we support the conclusion that pyloroplasty alone has little effect. The addition of vagotomy caused marked and significant acceleration of the rate at which the liquid meal emptied but was without effect on the rate of emptying of the solid meal. Clearly, the presence of the antrum, albeit denervated, accounts for the difference seen between this group of dogs and the previous group discussed above in whom prior antrectomy had been performed. Again, the mechanism by which the protective effect of the antrum is brought about is not clear. A reasonable assumption is that the denervated antrum is still capable of exerting controlling effect if the pyloric sphincter has been destroyed by pyloroplasty. Alternatively, solubilization of a solid meal may be impaired following vagotomy and antrectomy perhaps due to loss of the milling action of the antrum as well as impaired acid and pepsin secretion. Malgelada[8] has recently shown the solubilizing action of gastric secretion during a meal. Changes in acidity or in gastrin release cannot explain these differences. Both acid secretion and gastrin release in response to feeding should be higher after vagotomy and pyloroplasty than after vagotomy and antrectomy. Acid and gastrin are two factors known to inhibit gastric emptying.

Vagotomy alone, unaccompanied by pyloroplasty or antrectomy, markedly inhibited the emptying rate of both liquids and solids. The accelerating effect of vagotomy on emptying of liquids requires destruction of the antropyloric mechanism to uncover it. The vagally denervated pylorus is a major impediment to emptying of liquids. This aspect has not been stressed previously. The pylorus as a primary mechanism in the control of gastric emptying was discounted by Thomas.[9] Recently, however, Andersson and Grossman,[1] Isenberg and Csendes,[6] and Fisher and Cohen[3] have found that the pylorus of dog and man is characterized by a high pressure zone which responds to various stimuli. It relaxes in response to peristalsis, and contracts in response to acid, fats, amino acids, and glucose. Both secretin and cholecystokinin augment pyloric sphincter pressure. Gastrin alone does not increase pyloric sphincter pressure, but it antagonizes the effect of secretin and cholecystokinin.[4] Although we did not measure the pressure profile of the pyloric sphincter in these dogs, we suspect that vagotomy resulted in tonic contraction of the pyloric sphincter such that even the emptying of liquids after vagotomy was inhibited. With respect to the emptying of solids, Dozois et al.[2] have suggested that the pyloric sphincter may play some role. Whatever the role of the pylorus in gastric emptying may be under physiological conditions, our data clearly show that after vagotomy, the pylorus acts as a major obstruction to gastric emptying of both liquids and solids. This fact has been well appreciated by the surgeon who has found it necessary to employ a drainage procedure following truncal vagotomy.

Acknowledgments

We are grateful to Mr. K-L Leung for expert technical assistance and to Miss Gayle Henderson for typing the manuscript.

References

1. Andersson, S. and Grossman, M. I.: Profile of pH, Pressure, and Potential Difference at Gastroduodenal Junction in Man. Gastroenterology, 49:364, 1965.
2. Dozois, R. R., Kelley, K. A. and Code, C. F.: Effect of Distal Antrectomy on Gastric Emptying of Liquids and Solids. Gastroenterology, 61:675, 1971.
3. Fisher, R. and Cohen, S.: Physiological Characteristics of Human Pyloric Sphincter. Gastroenterology, 64:67, 1973.
4. Fisher, R. and Cohen, S.: The Hormonal Regulation of Pyloric Sphincter Function. J. Clin. Invest., 52:1289, 1973.
5. Gleysteen, J. J., Burdeshaw, J. A. and Hallenbeck, G. A.: Gastric Emptying of Liquids After Different Vagotomies and Pyloroplasty. Surg. Gynecol. Obstet., 142:41, 1976.
6. Isenberg, J. I. and Csendes, A.: Effect of Octapeptide of Cholecystokinin on Canine Pyloric Pressure. Am. J. Physiol., 222:428, 1972.
7. Ludwich, J. R., Wiley, J. N. and Bass, P.: Gastric Emptying Following Finney Pyloroplasty and Vagotomy. Am. J. Dig Dis., 15:347, 1970.
8. Malagelada, J. R.: Gastric Solubilization and Emptying of Digestible Solids After an Ordinary Meal in Man. Gastroenterology, 70:913, 1976.
9. Thomas, J. E.: Mechanisms and Regulations of Gastric Emptying. Physiol. Rev., 37:453, 1957.
10. Wilbur, B. G. and Kelly, K. A.: Effect of Proximal Gastric Complete Gastric, and Truncal Vagotomy on Canine Gastric Electric Activity, Motility and Emptying. Ann. Surg., 178:295, 1973.

Studies in Pharmacokinetics and Tolerance of Substances Temporarily Retained in the Liver by Microsphere Embolization

BO LINDELL, M.D., KARL-FREDRIK ARONSEN, M.D., BERTIL NOSSLIN, M.D., ULF ROTHMAN, M.D.

Earlier investigation has shown that a temporary arrest of arterial blood flow can be achieved by embolization with degradable microspheres. This study was made to investigate the change in pharmacokinetics and drug tolerance which takes place when a substance is retained in the liver by a microsphere embolization. ^{14}C-labelled inulin and 5-fluoro-uracil were studied. The administration of these substances with microspheres led to a delay in their systemic distribution. Furthermore there was an increased tolerance to 5-fluoro-uracil, probably due to a prolonged first pass effect when the substance was temporarily retained in the liver by a microsphere embolization.

THE THERAPEUTIC EFFECT of drugs is firmly tied to their pharmacokinetics. According to Notari,[9] an ideal drug should: a) reach the site of action, b) arrive rapidly and in sufficient quantity, c) remain for a sufficient length of time, d) be excluded from other sites and e) be removed from the target site at the right time. These properties can be assured by chemical modification of the drugs. Another way may be to deliver the drug directly to the target organ and hold it there for as long as necessary. By means of arterial regional infusion, drugs can be delivered to the target organ and can reach a high local concentration. This type of administration is used most commonly in the treatment of malignancy with cytotoxic drugs where the toxic side effects prevent a high systemic dosage.

With the introduction of a new type of degradable microsphere, it has become possible to achieve a temporary arterial flow reduction in a localized area or organ by intra-arterial embolization of microspheres. This means that a substance could be retained in the organ for a longer time, which might change both its therapeutic effects and its toxicity.

From the Experimental Department, the Department of Nuclear Medicine and the Department of Surgery, University of Lund, Malmö General Hospital, Malmö, Sweden

The aim of this study was to investigate the retention of inulin in the liver when injected simultaneously with degradable microspheres. Furthermore, the tolerance to a cytotoxic substance (5-fluoro-uracil) was studied under the same conditions.

Materials and Methods

The experiments were made on male Wistar–Fur rats (S.P.F. Möllegaard, Denmark) weighing 250–350 g. All animals were anesthetized by intraperitoneal injection of chloral hydrate 35 mg/100 g rat, 15 minutes before the experiment.

Forty-two rats were used to study the pharmacokinetics of inulin when injected into the liver artery, alone (21 animals) or in combination with microspheres (21 animals). In five rats from each group, blood and urine concentration of inulin were followed for 35 minutes after administration. The other 16 rats in each group were used for analysis of the inulin level in the liver parenchyma. These rats were killed at different intervals (2, 15, 30, and 60 minutes) after the administration of inulin, and the liver taken for examination.

Inulin (NEC–164 P Inulin carboxyl-^{14}C, New England Nuclear Corp., Boston) was purchased in aqueous solution of 1.96 mg/ml with a radioactivity of 5 μCi/ml. In every experiment 0.5 ml of this solution was injected.

To study drug tolerance, 5-fluoro-uracil (Roche) 300 mg/kg rat was injected into the liver artery without and in combination with microspheres. Eighteen rats were given 5-FU alone, and 16 rats were injected with the 5-FU-microsphere combination. White blood

---

Reprint requests: Dr. Bo Lindell, Department of Surgery, University of Lund, Malmö General Hospital, Malmö, Sweden.

Supported by grants from Pharmacia AB, Uppsala, Sweden, and from Styrelsen för Teknisk Utveckling, Stockholm.

Submitted for publication: March 7, 1977.

0003-4932-78-0100-0095-0075 © J.B. Lippincott Company

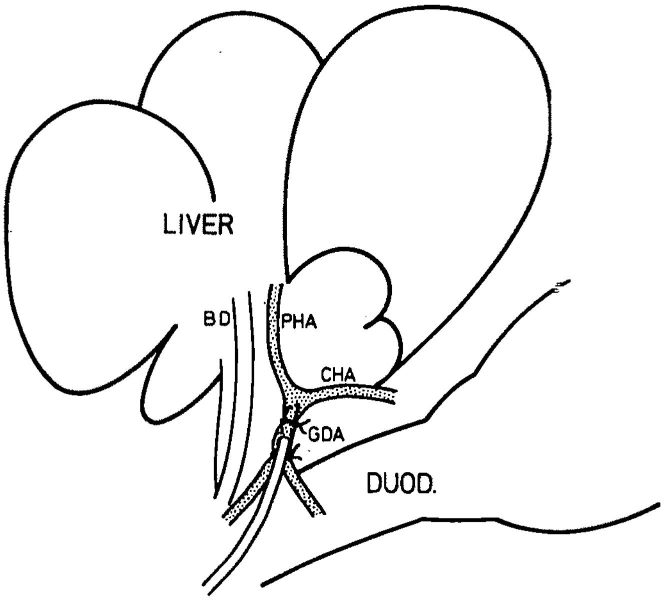


FIG. 1. Position of catheter for injection of test substances into the liver artery. PHA = Proper Hepatic Artery. CHA = Common Hepatic Artery. GDA = GastroDuodenal Artery. BD = Bile Duct

cell count, body weight and survival were registered every day for two weeks.

Administration of Test Substances

The injection of test substances into the liver artery was made through a retrograde catheter in the gastroduodenal artery (Fig. 1) according to a model described previously.[7] To prevent reflux to the common hepatic artery, this artery was occluded by a string during the injection. The catheter was then flushed with 0.2 ml heparinized saline (500 U Heparin Vitrum/100 ml saline).

Degradable Microspheres

The particles used for embolization are spheres made by crosslinked polysaccharide derivatives (starch). The microspheres were produced and supplied by Pharmacia AB, Uppsala, Sweden, and investigation at their laboratories has shown the following properties of the particles: The microspheres are completely digested by endohydrolases (amylase) in body fluids. Degradation time is dependent on the degree of cross-linking in the microsphere and the enzyme concentration. Furthermore, the size and number of microspheres injected will influence the time for flow retardation. The particles are built like a three dimensional network, and because of the configuration with a denser structure towards the surface of the sphere its size will remain intact until the final dissolution. During the disintegration the microspheres become plastic and may permit a plasma flow in the capillary bed.

The microspheres were delivered in batches of defined sizes and cross-linking levels. In this investigation a microsphere 19 ± 3.1 μm in size and with 420 × 10^6 microspheres per gram was used. The half time *in vitro* of this microsphere is nine minutes at amylase 25 μkat./l (Batch Ph BR 42 B 19B 92789 b).

The microspheres were kept dry and added to the solution to be injected just before use. The suspension was then vigorously vibrated. A concentration of 2 g% (w/v) microspheres was used. Inulin was injected in a volume of 0.5 ml which gave 42 × 10^4 spheres per injection when the microsphere combination was tested. To reach the toxic 5-FU dose (75 mg/250 g rat), 1.5 ml 5-FU solution (Roche) was needed, resulting in 126 × 10^4 spheres per injection.

Urine Sampling

Urine was collected during five minute periods via a plastic catheter (PE 10 Intramedic) introduced into the left ureter and fixed in place with a ligature. To facilitate the urine collection and to control all filtrated inulin, a right nephrectomy was performed. Diuresis was initiated 15 minutes before injection of the test substance by an intravenous injection of 2 ml 25% mannitol.

Blood Sampling

The rats undergoing the pharmacokinetic study with inulin had their tail artery catheterized (PE 50 Intramedic, Clay-Adam) to facilitate blood sampling. The blood was collected in 50 μl disposable pipettes and immediately transferred to the counting vials. Blood was sampled every 15 seconds during the first minutes. When examining the tolerance to 5-FU, 50 μl blood was collected once a day from a cut in the tail and used for counting white blood cells.

Sample Preparation and Measurement of Radioactivity

The different samples for measurement of inulin-carboxyl-^{14}C activity were prepared as follows: to 50 μl blood was added 0.4 ml 35% hydrogen peroxide and 1 ml of a 1/1 mixture of Soluene 100 (Packard Instrument Co., Inc., solubilizer) and isopropanol. Fifteen minutes later 10 ml Insta-Gel (Packard Instrument Co., Inc.) with 0.5 ml hydrochloric acid (0.5 normal) was added and the sample was then ready for counting. The urine which was collected during five minute periods was prepared by adding 10 ml Insta-Gel. The liver samples were weighed and cut into

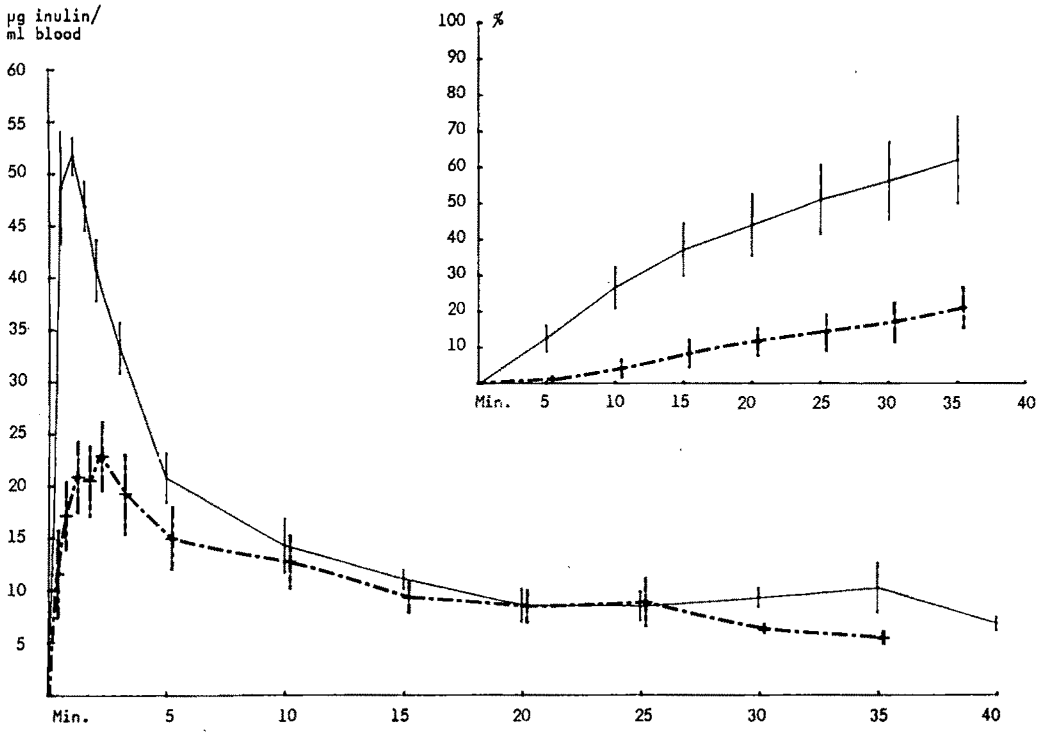


FIG. 2. Mean ^{14}C-inulin concentration (±SE) in blood. Solid line = after injection of 980µg inulin into liver artery. Broken line = after injection of 980 µg inulin and microspheres into liver artery. Chart top right shows renal inulin excretion in percentage of administered dose.

small pieces and then dissolved at 50° in Soluene 350 (Packard Instrument Co., Inc.) using 10 ml Soluene per gram liver tissue. After two days, 1 ml of this homogenized solution was diluted with 15 ml Insta-Gel and measured for activity.

The samples were measured in a liquid scintillation counter (LKB Wallac LSC 81000). The counting efficiency was determined with internal standard, and each sample count was corrected for quenching. The sample was measured for activity during a period of six minutes and a minimum net count of 1000 cpm was registered in every sample.

Results

The injection of inulin into the liver artery gave a rapid elevation of the inulin blood concentration to a maximum of 50–55 µg/ml blood in one minute (Fig. 2). The concentration then rapidly fell to a level of about 10 µg/ml blood after 20 minutes. The inulin was excreted with the urine, and after 35 minutes more than 60% of the administered dose was collected in the urine (Fig. 2).

When inulin was injected in combination with microspheres, the initial high peak concentration failed to appear, and the maximum blood concentration reached was 20–25 µg/ml blood. This difference was significant at 1% level. Twenty minutes after administration, the concentration curve in the blood was almost identical to the concentration found when inulin was injected alone (Fig. 2). The injection of inulin with microspheres also led to a significantly (at 1% level) delayed excretion of inulin with the urine, and after 35 minutes only 20% of the administered dose was found in the urine (Fig. 2).

Injection of inulin with microspheres resulted in an increased inulin concentration in the liver. During the first 30 minutes after injection of inulin and microspheres, the mean inulin concentration in the liver was raised by 42% (significant at 5% level, t = 1.86; one tail test) as compared to when inulin was injected alone (Fig. 3).

Injection of 5-FU alone caused a leukocytopenia in the rats. When 5-FU was administered with microspheres, leukocytopenia was less marked and was, furthermore, reversed at days four and nine when a significantly (at 1% level) higher number of circulating leukocytes was found than when 5-FU was injected alone (Fig. 4).

The 5-FU injection caused a decrease in the body weight with the most marked weight loss during the first four days. No significant difference was found. No difference was found when microspheres were added at the injection (Fig. 5).

The survival rate after this toxic dose of 5-FU showed a striking difference in the two groups. The survival rate in the group given 5-FU alone was 22% as compared to 75% when the drug was injected with microspheres (Fig. 6) and the difference was

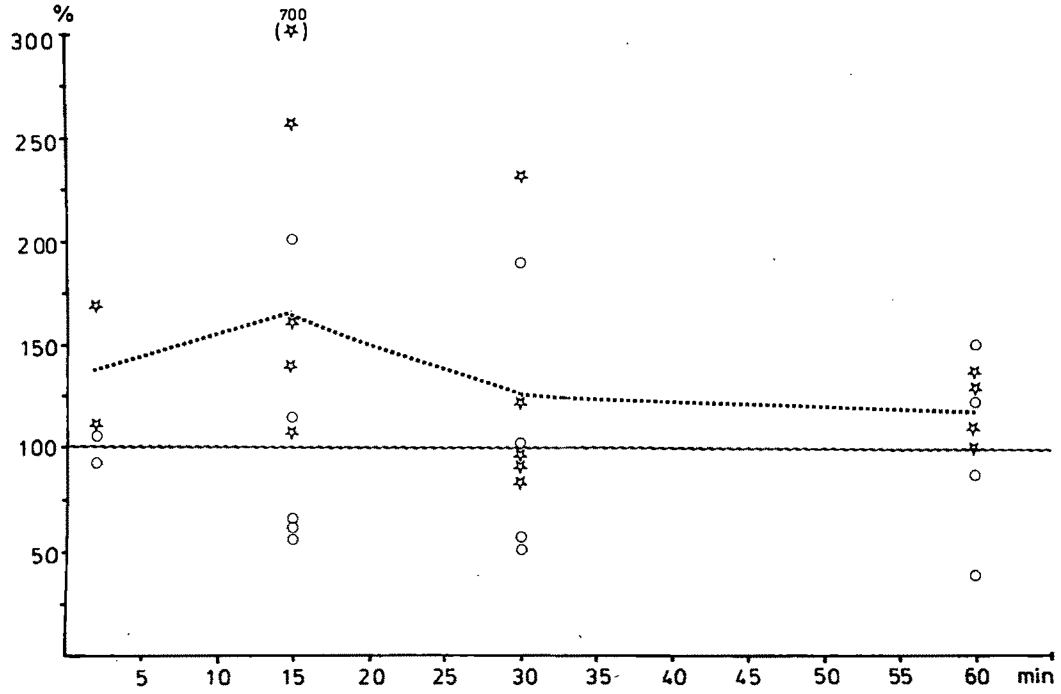


FIG. 3. Comparison of inulin amount in liver parenchyma when injected alone (Individual score = O Mean = wavy line) and in combination with microspheres (Individual score = star Mean = broken line). The points are calculated as percentage of the mean inulin value (set at 100%) reached each time after inulin is injected alone.

significant at 1% level (Chi square with Yate correction 7.47).

Discussion

Injection of a substance into the liver artery together with microspheres causes a delay in the distribution of the substance in the body. Because of slow release, the initial blood peak concentration will be reduced. The delay in the systemic distribution will then be influenced by the diffusion properties of the retained substance, affecting the portal washout during the arterial occlusion. This will mean that the microsphere

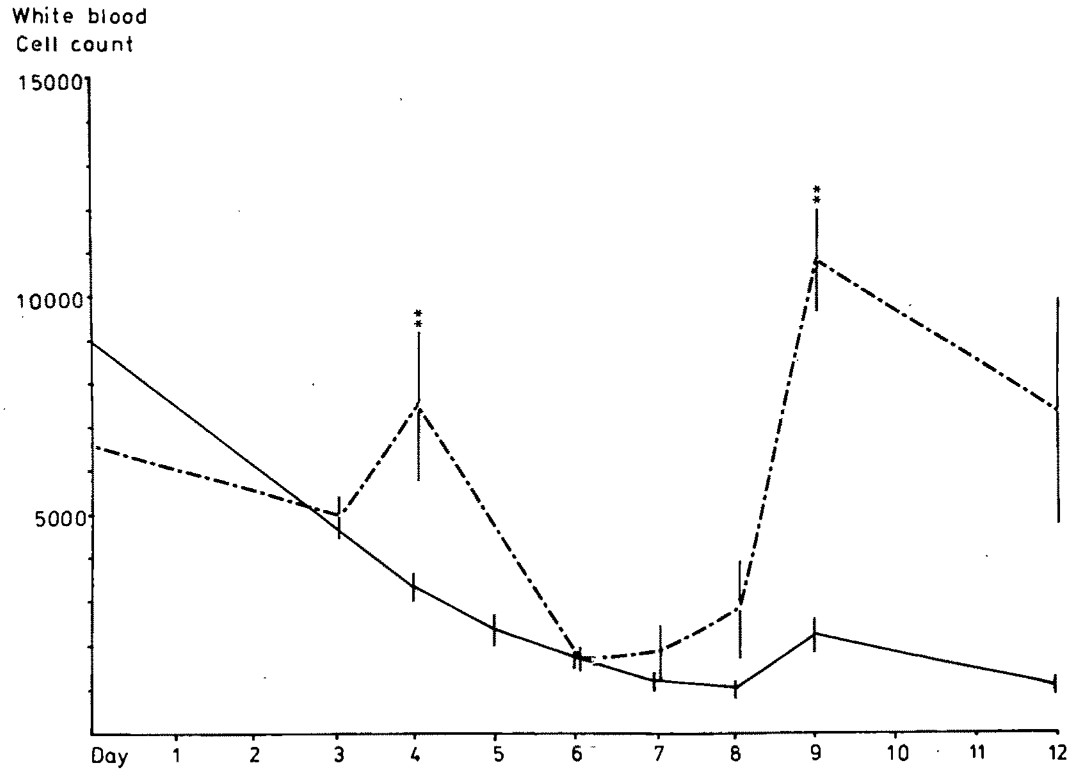


FIG. 4. Mean white blood cell count (±SE) after injection of 5-FU (300 mg/kg) into liver artery. Solid line = 5-FU. Broken line = 5-Fu + microspheres.

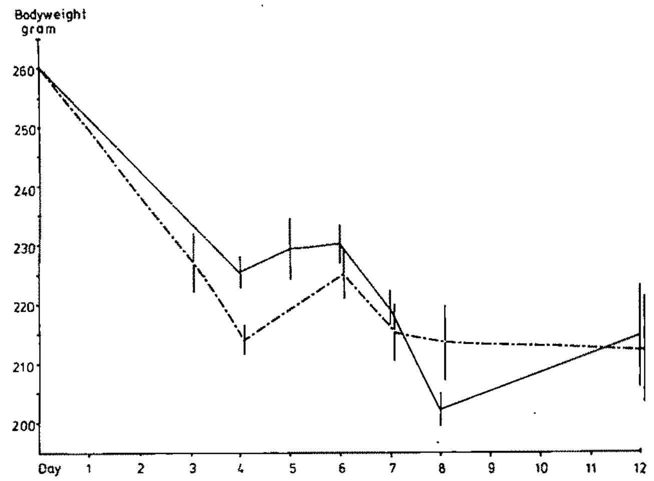


FIG. 5. Mean body weight (±SE) after injection of 5-FU (300 mg/kg) into liver artery. Solid line = 5-FU. Broken line = 5-FU + microspheres.

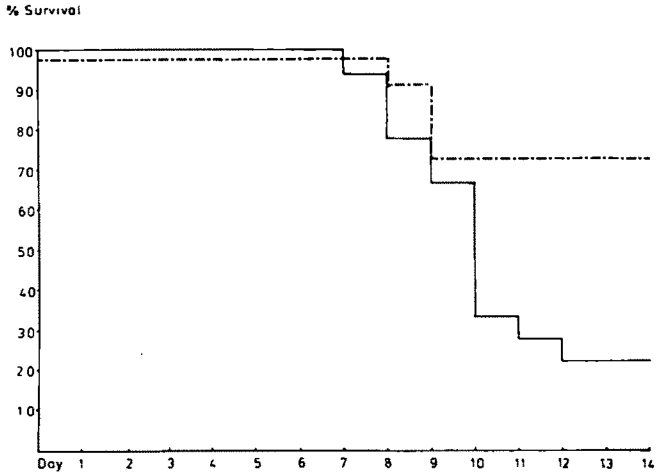


FIG. 6. Survival after injection of 5-FU (300 mg/kg) into liver artery without (Solid line) and in combination with microspheres (Broken line).

embolization will cause only a minor delay in the washout of a highly diffusible substance like xenon.[8]

The regional drug metabolism will also be decisive for the systemic distribution of a drug delivered directly to the liver. Substances metabolized in the liver and excreted by the bile will be reduced in systemic availability after passage through the liver. The first pass effect may then be increased when the liver contact is prolonged, as will be the case when drugs are administered with microspheres. Inulin is, however, not metabolized in the liver or excreted by the bile, and the reduced activity found in blood and urine after administration together with microspheres is, therefore, thought to depend on a slow release effect in the liver.[4]

Since 5-FU is a substance which is mainly metabolized in the liver, the first pass effect will be valid for this drug.[2,5] The depression of the bone marrow activity after a single dose of this drug appears to be related to the early plasma concentration.[3] Correspondingly, retention of the drug in the liver by microspheres gives a reduced depression of the bone marrow as revealed by the white blood cell count. The reduced leukopenia when 5-FU was administered with microspheres is probably also the reason why the survival increased after this treatment as compared to when 5-FU was injected alone. The gastrointestinal toxic effect sometimes observed after 5-FU treatment, with diarrhoea and loss of appetite, was not prominent in either group, and the body weight developed identically after the 5-FU injection whether or not the microspheres were added.

The change in drug tolerance which can be affected by microsphere administration depends on the metabolic pathway of the drug. The ideal drug for this administration into the liver would then be a cytotoxic substance with a high affinity to tissues in the liver, where it is degraded to atoxic metabolites. There is evidence that chemotherapy infusion with simultaneous tumor blood flow restraint is highly injurious to tumor cells,[1] and that microsphere embolization can be repeated several times. Liver retention of the appropriate drug would through concomitant microsphere injection then be an effective new approach to the treatment of liver malignancy.

References

1. Baba, T., Aoki, K., Kidera, Y., et al.: Temporary Interruption of Regional Blood Flow Combined with Local Hyperthermia for Cancer Chemotherapy. Cancer Res., 36: 2146, 1976.
2. Clarkson, B., O'Connor, A., Winston, L. R. and Hutchison, D.: The Physiologic Disposition of 5-fluoro-uracil and 5-fluoro-2-deoxyuridin in Man. Clin. Pharm. Ther., 5:581, 1964.
3. Cohen, J. L., Irwin, L. E., Marshall, G. J., et al.: Clinical Pharmacology of Oral and Intravenous 5 Fluorouracil. Cancer Chemother. Rep., 58:723, 1974.
4. Eriksson, H., Hellström, W. and Ryrfeldt, Å: The Biliary Excretion of ^{3}H-inulin and ^{3}H Terbutaline in the Unanesthetized Rat. Acta Physiol. Scand., 95:1, 1975.
5. Finn, C. and Sadee, W.: Determination of 5-Fluoro-uracil Plasma Levels in Rats and Man by Isotope Dilution-mass Fragmentography. Cancer Chemother. Rep. 59:279, 1975.
6. Gibaldi, M. and Perrier, D.: Route of Administration and Drug Disposition. Drug Metab. Rev. 3:185, 1974.
7. Lindell, B.: A Model for Liver Artery Infusion in the Rat. Submitted for publication.
8. Lindell, B., Aronsen, K. F. and Rothman, U.: Repeated Embolization of the Liver Artery by Degradable Microspheres in the rat. Submitted for publication.
9. Notari, R.: Structural Effects in Pharmacokinetics and Drug Response. Symposium on Pharmacokinetics and Drug effects, Stockholm, Nov. 1974. Acta Pharmac. Suecia, 11:633, 1974.

Techniques in Surgery

The Clinical Use of the Naso-gastric Duodenal Mercury Tip Sump Tube in Abdominal Surgery and in the Management of Intestinal Obstruction

JOSEPH HODGE, M.D.

From the Department of Surgery,
Spartanburg General Hospital,
Spartanburg, South Carolina

A naso-gastric duodenal mercury tip weighted sump tube has been developed that will efficaciously decompress small bowel in cases of paralytic ileus, partial or complete mechanical obstruction, and can easily be introduced into the duodenum by a nurse, house staff or attending physician. The tube also may be used for diagnostic purposes to obtain gastrointestinal, pancreatic or biliary secretions.

SINCE INTESTINAL OBSTRUCTION is a condition frequently requiring decompression, the conservative treatment usually consists of intubation,[1-4] colonic irrigation, replacement of fluid and electrolytes. Complete mechanical intestinal obstruction requires surgical intervention[5,6] in order to prevent strangulation, gangrene and severe metabolic derangement. Because adequate decompression through the usual measures are partially effectual, the author developed a simple naso-gastric duodenal mercury slightly curved weighted tip tube that can be easily introduced into the duodenum by a nurse, house staff or attending physician.

Materials and Methods

The decompressive tube is 125 cm long and contains a 12.5 cm mercury tip that is slightly curved and weighted measuring the diameter of an 18 French catheter (Fig. 2). The tube (Fig. 1) consists of a ventral aspirating lumen with a funnel connector to the wall suction and a vent tube running along the base of the main lumen through which air or saline is introduced to free particulate matter from the perforation measuring 12.5 cm proximal to the weighted tip.

Discussion

The NGD mercury tip tube is indicated in preparation for certain abdominal surgical conditions such as cholecystectomy, gastric resection, small and large bowel resection, ventral herniorrhaphy, paralytic ileus, and small and large bowel mechanical obstruction. The tube may be used to obtain gastro-intestinal, biliary

---

Reprint requests: Dr. Joseph Hodge, M.D., Hodge Building, 856 N. Church Street, Spartanburg, South Carolina 29303.

Submitted for publication: April 2, 1977.

0003-4932-78-0100-0100-0060 © J.B. Lippincott Company

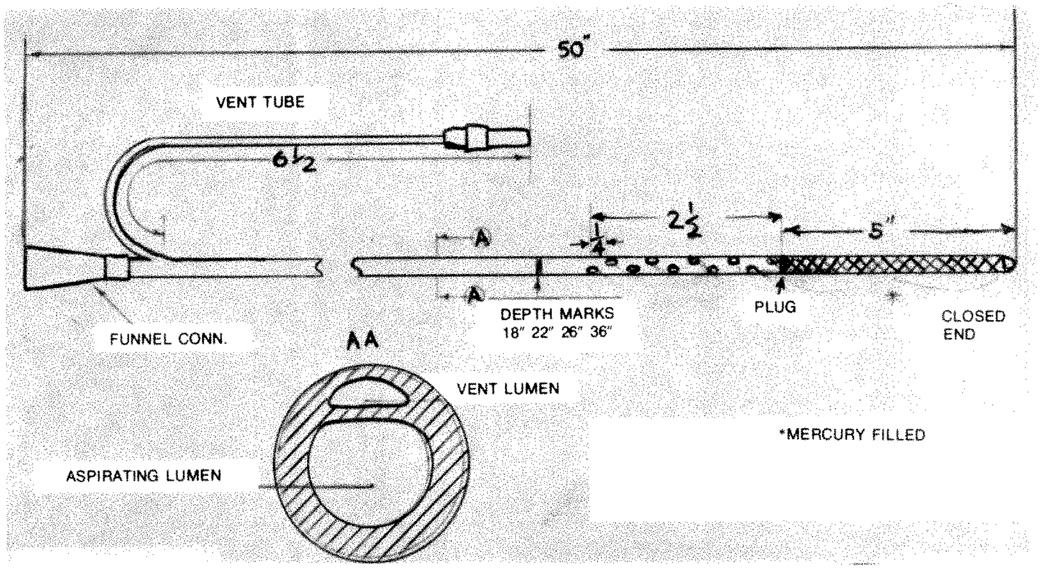


FIG. 1. Intestinal Decompressor: mercury weighted tip.

and pancreatic secretions for diagnostic purposes. The device is easily passed by way of the naso-gastric route by nurse, house staff or attending physician. For decompression of the stomach, the tube may be passed to 35 cm, and by advancing it to 50 cm the tube will be positioned into the duodenum (Fig. 3). If difficulties are encountered, with the patients on their right side and with the aid of fluoroscopy, the

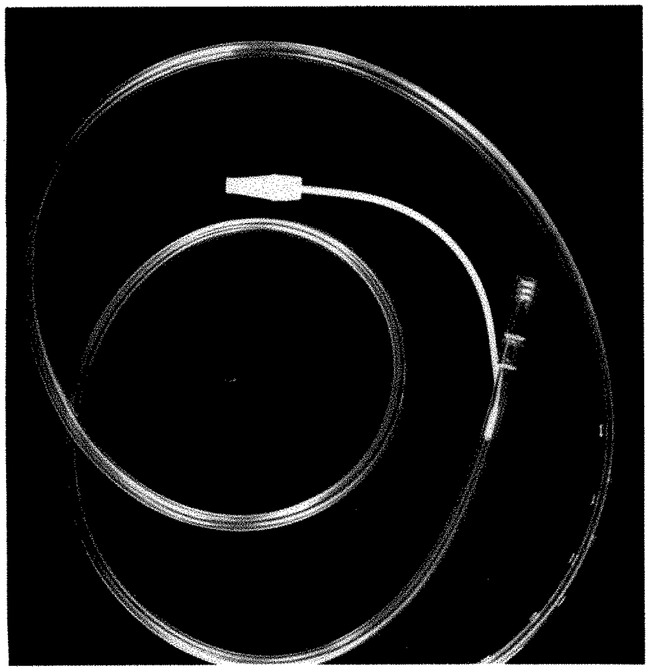


FIG. 2. Intestinal decompressor a mercury weighted tip.

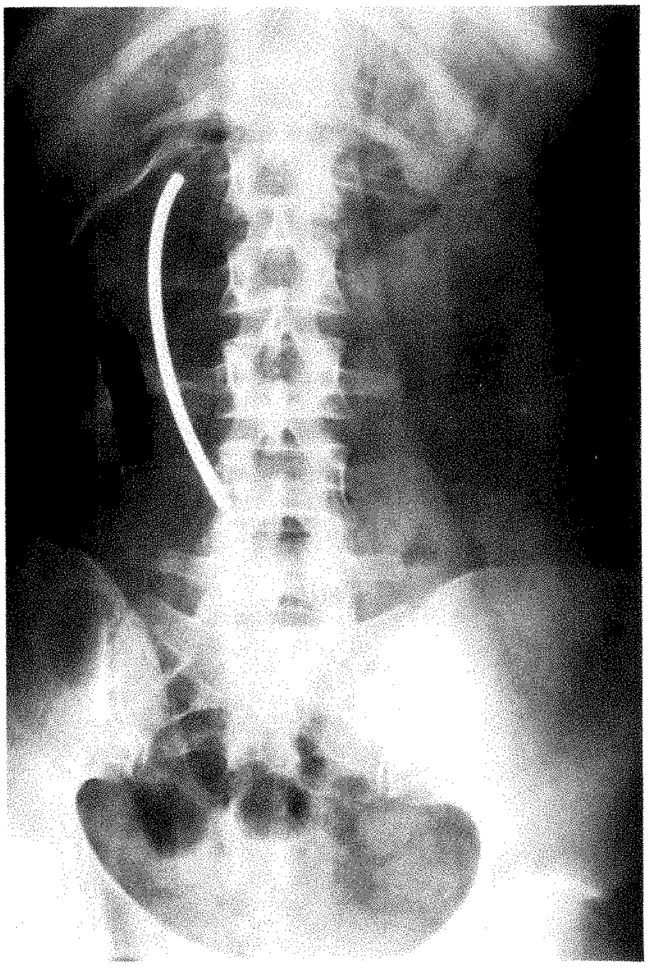


FIG. 3. Intubation of duodenum.

proximal end of the naso-gastric duodenal sump tube can be passed directly into the duodenum. The patients are then turned to the supine position. Slack is left in the tube and it is not taped to the nose or face but allowed to progress under peristalic movements distally into the small intestines. The tube may be irrigated by introducing 15 cc to 20 cc of normal saline into the main portion of the tube connected to suction by disengaging it from suction and 5–10 cc of air is introduced into the air vent every hour. This prevents particulate matter from plugging up the suction lumen.

Summary and Conclusion

The NGD mercury weighted tip sump tube is simple, efficacious and especially useful in the management of patients with partial or complete mechanical obstruction, and in many cases spares the patient surgical intervention.

References

1. Abbott, W. O.: Indications for the Use of The Miller-Abbott Tube. N. Engl. J. Med., 225:641, 1941.
2. Cantor, M. O.: Mercury-Its Role in Intestinal Decompression Tubes. Am. J. Surg., 73:690, 1947.
3. Devine, J. W. and Devine, J. W. Jr.: Duodenal Intubation. Surgery, 33:513, 1953.
4. Harris, F. I.: Intestinal Intubation in Bowel Obstruction: Technic with New Single Lumen Mercury Weighted Tube. Surg., Gynecol. Obstet., 81:671, 1945.
5. Hodge, J.: An Enterotomy–Colotomy Decompressor for The Treatment of Intestinal Obstruction. Am. J. Surg., 96:3: 428, 1958.
6. Hodge, J.: The Long Arm Enterotomy–Colotomy Decompressor in The Surgical Management of Intestinal Obstruction. J. S. C. Med. Assoc., 60:217, 1964.

AX8™

AFFILIATED/angēnieux AX8
SURGICAL LIGHT

The Affiliated/angēnieux AX8 solves the most perplexing problems of conventional lighting systems.

SHADOWS:
The surgeon's head often casts a shadow with conventional lights. But the AX8's unique X-shape can be positioned around the surgeon's head to avoid shadows. Its compact size reduces shadows cast by other members of the OR team.

DRIFTING:
AX8's unique ball and-socket construction and unique counterbalancing system maintains the light where you set it for drift-free positioning without irritating interruptions for adjustments.

HEAT:
All surgical lights generate heat. But AX8 ventilates it outside the OR away from you and the surgical team.

COLOR DISTORTION:
AX8's patented coated mirror system reduces color distortion. Color corrected light reveals realistic tissue color.

LIGHT INTENSITY:
The AX8 is more compact than most conventional systems, but it delivers more light intensity to give you the illumination you need even in deep cavities. Intensity can be adjusted from 3,000 to 11,500 footcandles.

POSITIONING AND FOCUSING:
The lightweight AX8 gives you one simple positioning/focusing knob for fast, easy set-up. It's also more flexible than conventional track lighting. The AX8 can be positioned anywhere within a 13 foot diameter covering an area of 132.7 square feet in all.

MULTIPLE SOURCE ILLUMINATION:
The AX8 system enables you to add two or four pod satellites at any time after the original installation.

Consider all the advantages that Affiliated/angēnieux AX8 offers you. Shouldn't it be the light you work under?

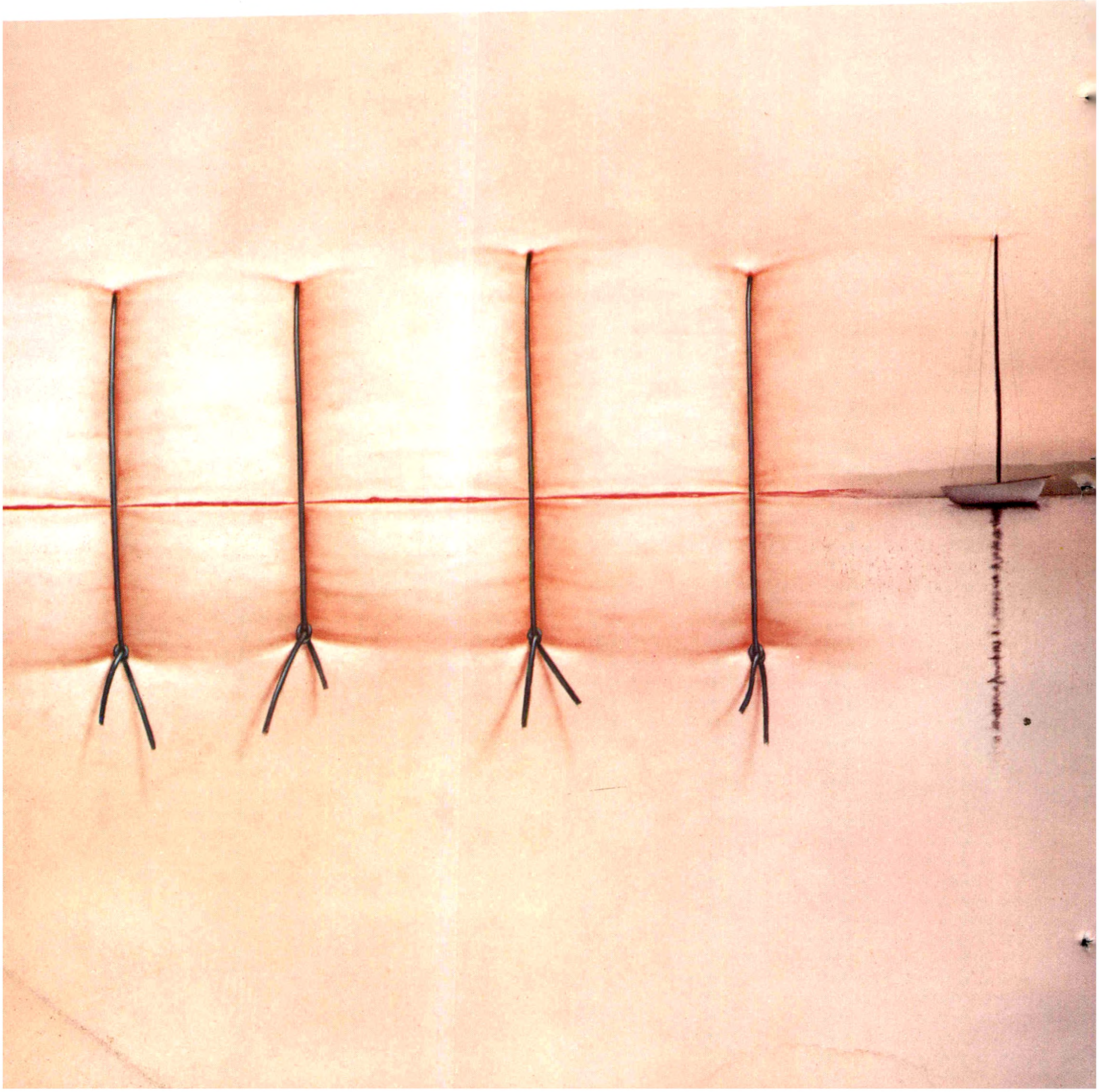
For more information call Wayne Goodear, toll free (800) 325-8860

AFFILIATED HOSPITAL PRODUCTS INC.
1920 South Jefferson Avenue St. Louis, Missouri 63104

it has long been recognized that anxiety, tension, agitation, and apprehension are all capable of increasing pain perception…"

Halpern, L. M.: Anxiety and pain in postoperative patients. Hospital Practice *(special report) January 1977, pp 31-33.*

Following surgery... he perception of pain diminished



Vistaril® I.M.
(hydroxyzine HCl)

by Calm

- reduces the anxiety component of pain
- permits reduction in narcotic dosage
- controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

© 1977, Pfizer Inc.

Vistaril® I.M.

(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

preoperatively and postoperatively

- allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain
- may enhance the effects of analgesics and reduce narcotic requirements
- controls postoperative emesis
- vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml—10 ml vial; 50 mg/ml—2 ml and 10 ml vial; Isoject® 25 mg/ml and 50 mg/ml, 1 ml fill; 100 mg/2 ml, 2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vial)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vial)

More detailed professional information available on request.

Pfizer
ABORATORIES DIVISION
PFIZER INC

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Tigan is indicated for the control of nausea and vomiting.

CONTRAINDICATIONS: The injectable form of Tigan in children, the suppositories in premature or newborn infants, and use in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.

WARNINGS:

> Caution should be exercised when administering Tigan to children for the treatment of vomiting. Antiemetics are not recommended for treatment of uncomplicated vomiting in children and their use should be limited to prolonged vomiting of known etiology. There are three principal reasons for caution:
>
> 1. There has been some suspicion that centrally acting antiemetics may contribute, in combination with viral illnesses (a possible cause of vomiting in children), to development of Reye's syndrome, a potentially fatal acute childhood encephalopathy with visceral fatty degeneration, especially involving the liver. Although there is no confirmation of this suspicion, caution is nevertheless recommended.
> 2. The extrapyramidal symptoms which can occur secondary to Tigan may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy.
> 3. It has been suspected that drugs with hepatotoxic potential, such as Tigan, may unfavorably alter the course of Reye's syndrome. Such drugs should therefore be avoided in children whose signs and symptoms (vomiting) could represent Reye's syndrome. It should also be noted that salicylates and acetaminophen are hepatotoxic at large doses. Although it is not known that at usual doses they would represent a hazard in patients with the underlying hepatic disorder of Reye's syndrome, these drugs, too, should be avoided in children whose signs and symptoms could represent Reye's syndrome, unless alternative methods of controlling fever are not successful.

Tigan may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. Reye's syndrome has been associated with the use of Tigan and other drugs, including antiemetics, although their contribution, if any, to the cause and course of the disease hasn't been established. This syndrome is characterized by an abrupt onset shortly following a nonspecific febrile illness, with persistent, severe vomiting, lethargy, irrational behavior, progressive encephalopathy leading to coma, convulsions and death.

Usage in Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or stillborn pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.

PRECAUTIONS: During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

NOTE: The injectable form is intended for intramuscular use only; it is not recommended for intravenous use.

HOW SUPPLIED: Suppositories, Pediatric, 100 mg, boxes of 10. Suppositories, 200 mg, boxes of 10 and 50.

Ampuls, 2 ml, boxes of 10. Multiple-Dose Vials, 20 ml. Thera-Ject* (Disposable Syringes), 2 ml, boxes of 25. Capsules 250 mg, bottles of 100 and 500; 100 mg, bottles of 100.

Beecham
laboratories
Bristol, Tennessee 37620

Control post-op nausea & vomiting with non-phenothiazine

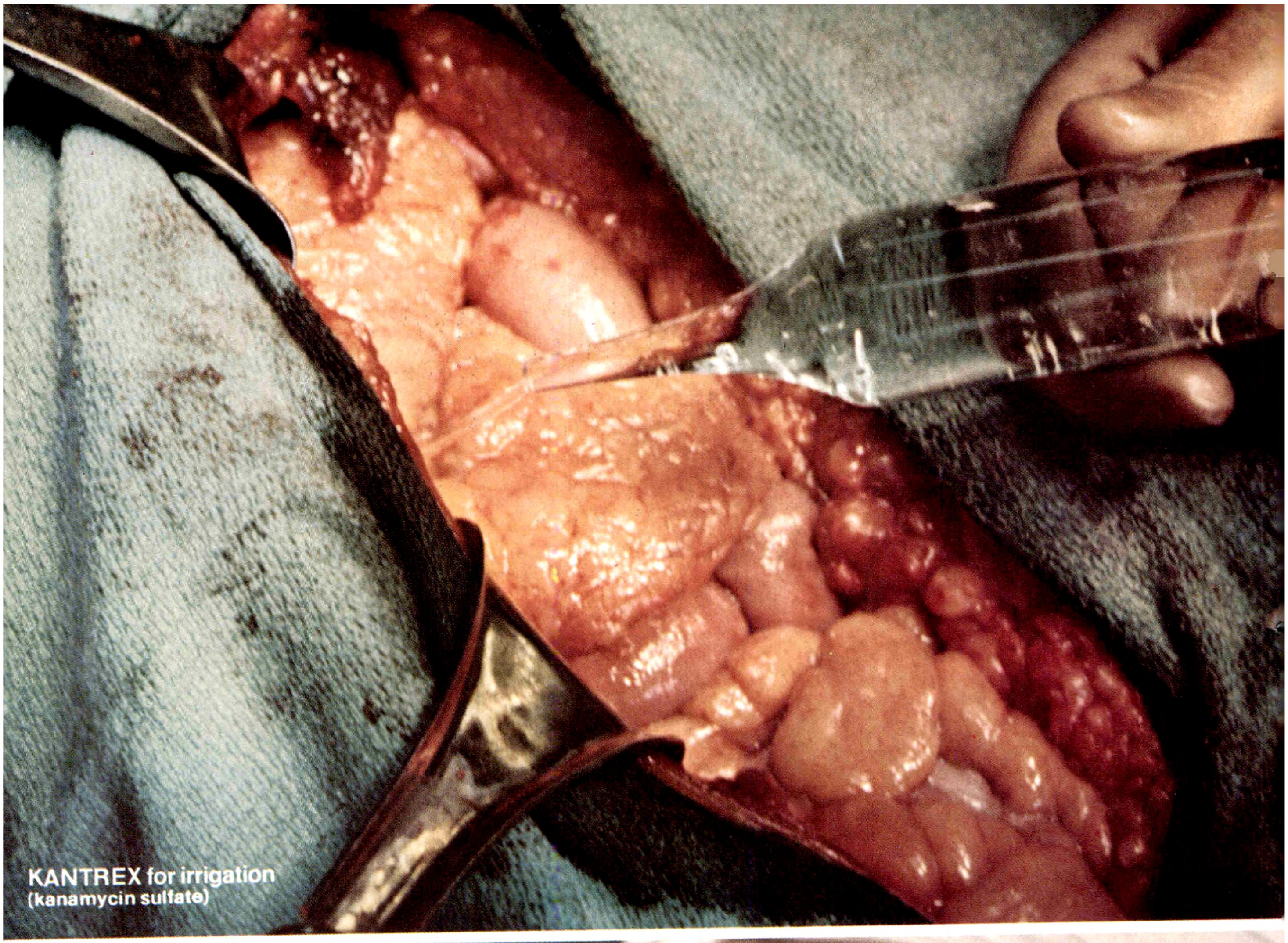
TIGAN®

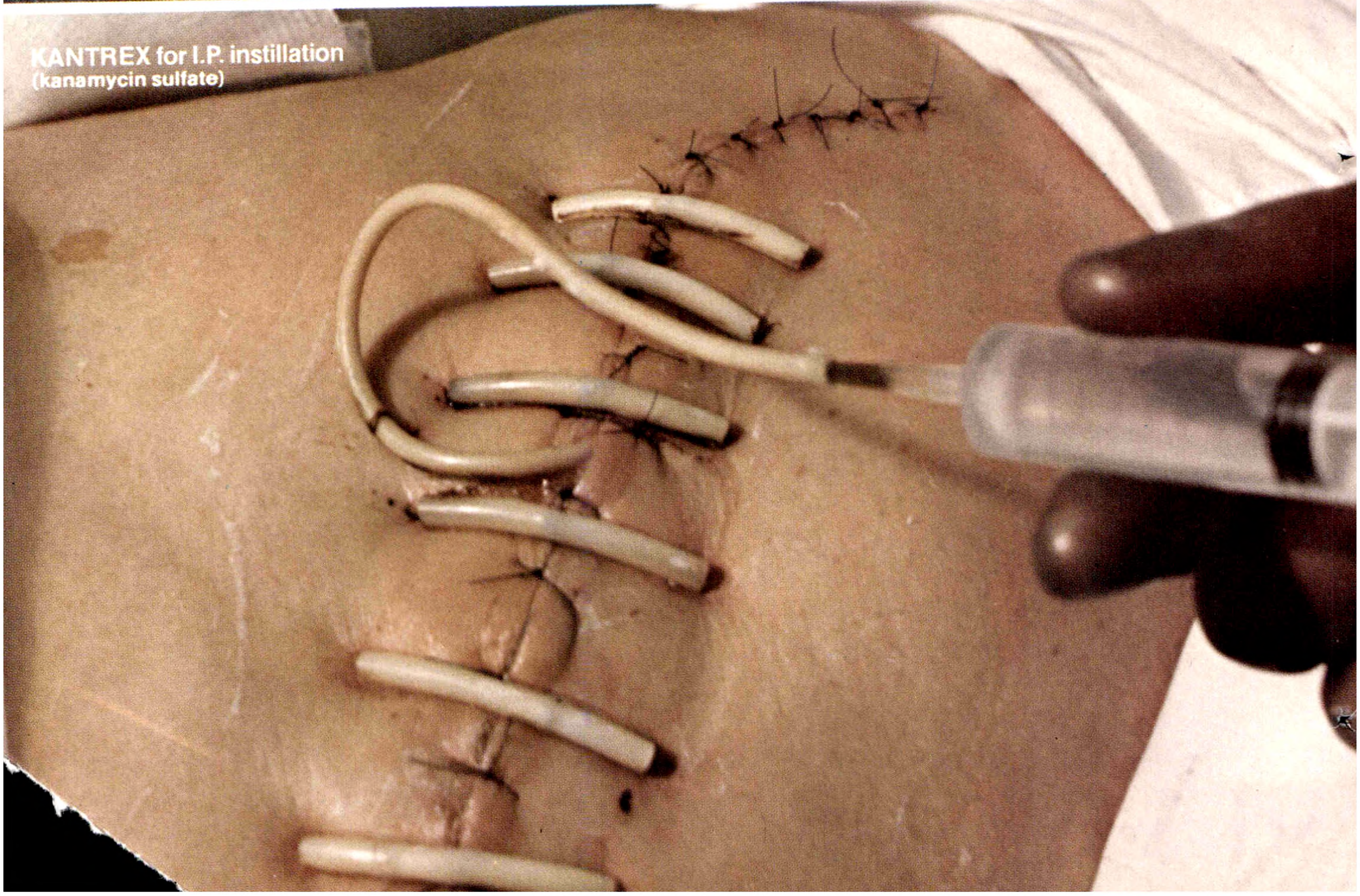
(trimethobenzamide HCl)

• **one indication:** specific for control of nausea and vomiting. (Not recommended for treatment of nausea and vomiting of unknown etiology in children.) • **acts promptly and gently.** • **infrequent side effects:** seldom severe enough to require discontinuation of therapy. Occasional reports have described hypersensitivity reactions and Parkinson-like symptoms. (See the Full Prescribing Information.) • **versatile dosage forms:** Thera-Ject®* Disposable Syringes: 100 mg/ml (2 ml) • Ampuls*: 100 mg/ml (2 ml) • Vials*: 100 mg/ml (20 ml) • Capsules: 250 mg and 100 mg • Suppositories*: 200 mg and 100 mg (pediatric)

*Tigan suppositories are contraindicated in premature and newborn infants. Tigan injectable is contraindicated in children.

Beecham
laboratorie
Bristol, Tennessee 37
Please see adjoin
for Brie


KANTREX for irrigation
(kanamycin sulfate)


KANTREX for I.P. instillation
(kanamycin sulfate)

Before peritoneal contamination due to fecal spill leads to peritoneal infection...

Kantrex®
(kanamycin sulfate) Injection I.M./I.V.

for intraperitoneal use/a surgical adjunct.

☐ more than a decade of clinical experience indicates the effectiveness of Kantrex® (kanamycin sulfate) in patients with peritonitis or peritoneal contamination.[1-7]

☐ Kantrex administration during surgery, or instillation post-op provides immediate contact with the site of existing or potential infection—permits higher local concentrations than can be achieved with systemic use, without increased risk of toxicity.

☐ absorption with intraperitoneal instillation of Kantrex is about the same as with intramuscular use, while absorption by irrigation is considerably less. High transient peritoneal concentrations have not resulted in any local tissue reactions.

☐ Kantrex—a preferred antibiotic with a precise mode of administration for patients with peritoneal soilage or peritonitis. Of course, *Kantrex should not be used for irrigation or instillation in a routine prophylactic manner;* its use is recommended *only* following exploration for established peritonitis or after peritoneal contamination due to fecal spill during surgery.

DOSAGE FOR INTRAPERITONEAL USE
KANTREX for irrigation

- Dilute contents of 500 mg. vial in 200 ml. Sterile Water for Injection.
- The resultant 0.25% solution (2.5 mg./ml.) may be used as an irrigant.

KANTREX for I.P. instillation

- Adults: 500 mg. diluted in at least 20 ml. sterile distilled water.
- Children: 7.5 mg./Kg. diluted in at least 20 ml. sterile distilled water.
- The above dosages have been repeated every 12 hours for up to 3 days.
- Total daily dosage by all routes should not exceed 1.5 Gm. for adults, or 15 mg./Kg. for children.
- Instill solution through polyethylene tube sutured into wound at closure. If possible, postpone instillation until patient has fully recovered from effects of anesthesia or muscle-relaxing drugs.
- Adjust dosage interval by "creatinine X 9" formula for patients with impaired renal function.*

*e.g.: If serum creatinine is 2 mg./100 ml., multiply by 9; interval between Kantrex doses is 18 hours.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
COMBINED KANTREX® INJECTION AND PEDIATRIC INJECTION
(kanamycin sulfate injection)

For complete information, consult Official Package Circular. (12) 6/25/75

Warning: The major toxic effect of parenterally administered kanamycin sulfate is its action on the auditory portion of the eighth nerve. High frequency deafness usually occurs first and can be detected by audiometric testing. Tinnitus or vertigo may occur and are evidence of vestibular injury and impending bilateral irreversible deafness.

In patients with impaired kidney function, the risk of severe ototoxic reactions and permanent deafness is sharply increased. In such cases, the daily dosage should be reduced and the interval between doses lengthened. If there is evidence of progressive renal dysfunction (increasing NPN, BUN, creatinine or oliguria) during therapy, audiometric tests are advised and discontinuation of the drug should be considered.

Older patients and patients receiving a total dose of more than 15 Gm. of kanamycin sulfate should be carefully observed for signs of eighth nerve damage.

Infants and children generally tolerate the drug well; and when the recommended precautions are followed, the incidence of toxic reactions is low.

Neuromuscular paralysis with respiratory depression may occur when kanamycin sulfate is administered intraperitoneally concomitantly with anesthesia and muscle-relaxing drugs. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug.

The concurrent systemic use of other ototoxic and/or nephrotoxic drugs, particularly streptomycin, polymyxin B, polymyxin E (colistin), neomycin, gentamicin, and viomycin should be avoided.

The administration of kanamycin sulfate and rapid acting diuretic agents, e.g. ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, and mannitol (particularly when the diuretic is given intravenously) may cause irreversible deafness. Concurrent use of these agents should be avoided. (See "Adverse Reactions.")

Usage in Pregnancy: Safety of this drug in human pregnancy has not been established.

Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other potentially ototoxic agents may be a contraindication if effective, alternative therapy is available.

THIS DRUG IS *NOT* INDICATED IN LONG-TERM THERAPY (e.g. Tuberculosis) BECAUSE OF THE OTOTOXIC HAZARD WITH EXTENDED ADMINISTRATION.

Warning: See "Warning" box above.

Precautions: Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex (kanamycin sulfate) if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occurs, discontinue therapy. Mycotic or bacterial superinfection may occur.

Adverse Reactions: Nephrotoxicity—albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity—see box warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

Dosage and Administration: The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult total daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gm.

The intravenous route is used only if intramuscular administration is not feasible. The 0.5 Gm. dose is added to the 200 ml. of sterile diluent and administered 60 to 80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

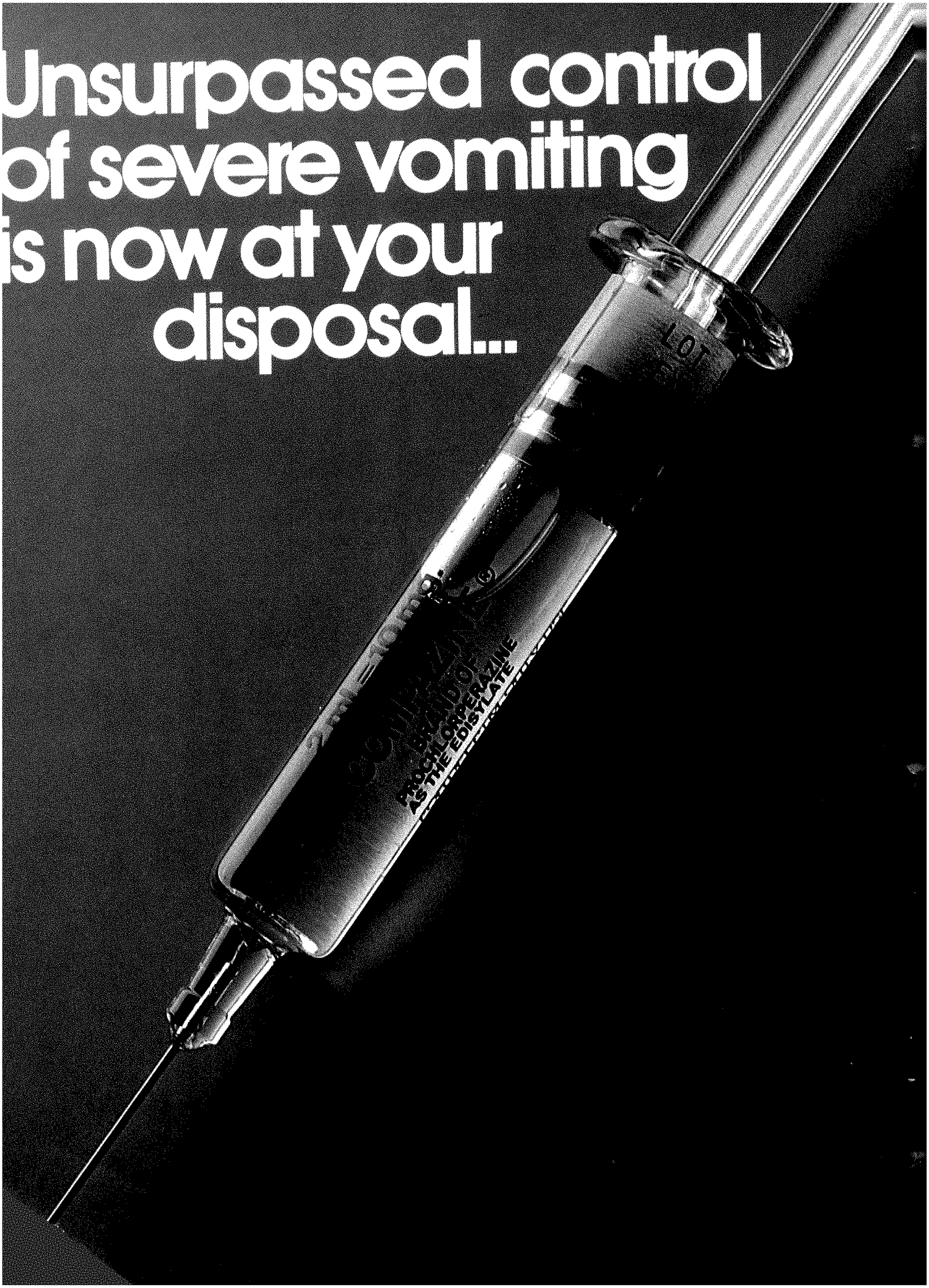
As aerosol treatment, 250 mg. of Kantrex is diluted with 3 ml. of physiological saline and nebulized.

Kantrex Injection in concentrations of 0.25 per cent (2.5 mg./ml.) has been used satisfactorily as an irrigating solution in abscess cavities, pleural spaces, peritoneal and ventricular cavities.

Supplied: Rubber capped vials as a ready-to-use sterile aqueous solution in two concentrations: 0.5 Gm. in 2 ml., 1.0 Gm. in 3 ml., Pediatric Injection 75 mg. in 2 ml.

References: 1. Cohn I Jr, et al: Intraperitoneal kanamycin—clinical experience. *Am Surg* 29:756-760, November 1963. 2. Cohn I Jr: Peritonitis: Prevention and cure. *J Fla Med Assoc* 56:705-708, September 1969. 3. Nelson JL, Kuzman JH, Cohn I Jr: Intraperitoneal lavage and kanamycin for the contaminated abdomen. *Surg Clin North Am* 55:1391-1395, December 1975. 4. Atkins RC, et al: Prolonged antibiotic peritoneal lavage in the management of gross generalized peritonitis. *Med J Aust* 1:954-956, 1976. 5. Brockenbrough EC, Moylan JA: Treatment of contaminated surgical wounds with a topical antibiotic: A do blind study of 240 patients. *Am Surg* 35:789-792, November 1969. 6. Cic PN, Malament M, Bellingham C: Surgical wound irrigation: Kanamy versus saline. *Urology* 3:63-66, January 1974. 7. Bingham R, Fle Church S: The local use of antibiotics to prevent wound infecti 99:194-200, March-April 1974.

BRISTOL LABORATOR
Division of Bristol-Myers Co


Unsurpassed control of severe vomiting is now at your disposal...
LOT
2 ml = 10 mg.
COMPAZINE®
BRAND OF
PROCHLORPERAZINE
AS THE EDISYLATE

'Compazine' pre-filled disposable syringe

- ready to use for prompt control of severe vomiting often accompanying drug therapy, adult surgery, cancer and other diseases
- 11 other dosage forms and strengths also available

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: To control severe nausea and vomiting. For the management of the manifestations of psychotic disorders.

Possibly effective: To control excessive anxiety, tension and agitation as seen in neuroses or associated with somatic conditions.

'Compazine' has not been shown effective in the management of behavioral complications in patients with mental retardation.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings:

Caution is recommended when 'Compazine' is administered for the treatment of vomiting in children.

Antiemetics are not recommended to treat uncomplicated short-term vomiting in children or vomiting of unknown etiology.

The possibility of extrapyramidal reactions from 'Compazine' may confuse the diagnosis of Reye's syndrome or other encephalopathy. Although unconfirmed, some suspicion exists that centrally-acting antiemetics may contribute to or adversely affect the course of Reye's syndrome, and should be avoided in suspected cases.

Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: Antiemetic effect may mask toxic drug overdosage or physical disorders. Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. In children with acute illnesses or dehydration, use only under close supervision.

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

SUPPLIED: TABLETS—5, 10 and 25 mg., in bottles of 100; **SPANSULE® CAPSULES**—10, 15, 30 and 75 mg., in bottles of 50; **INJECTION**—5 mg./ml. in 2 ml. ampuls and disposable syringes, and 10 ml. multiple-dose vials; **SUPPOSITORIES**—2-1/2, 5 and 25 mg.; **SYRUP**—5 mg./5 ml.; **CONCENTRATE** (intended for institutional use only)—10 mg./ml.; **SINGLE UNIT PACKAGES** of 100 (intended for institutional use only)—5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

Compazine® brand of **prochlorperazine**

Injection: 5 mg./ml.

the emesis nemesis

SK&F
a SmithKline Company

Smith Kline &French Laboratories Philadelphia, PA 19101

BURROUGHS WELLCOME CO. MAKES CODEINE COMBINATION PRODUCTS.

YOU MAKE THE CHOICE.

EMPIRIN® COMPOUND c̄ CODEINE #3

Each tablet contains:
codeine phosphate, 32 mg (gr ½),
(Warning: May be habit-forming);
aspirin, 227 mg; phenacetin, 162 mg;
and caffeine, 32 mg.

C III

EMPRACET™ c̄ CODEINE #3

Each tablet contains:
codeine phosphate, 30 mg (gr ½),
(Warning: May be habit-forming);
and acetaminophen 300 mg.

C III

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

29.11.78

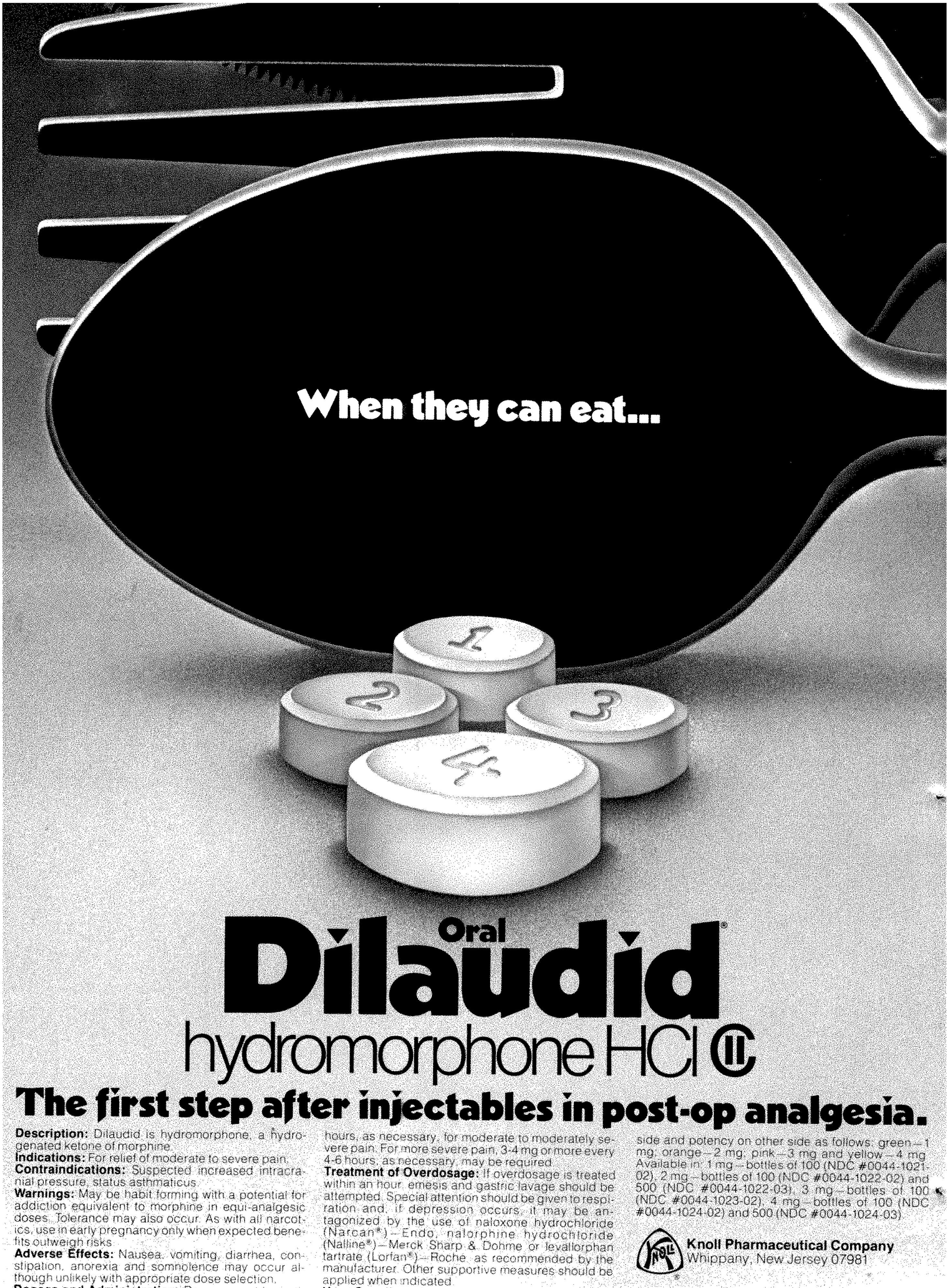
MAY 1978 • VOL. 187, NO. 5
ISSN 0003-4932 ANSUA5

ANNALS
of
SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

May and June numbers contain papers delivered at
THE 89TH ANNUAL SESSION
of the
SOUTHERN SURGICAL ASSOCIATION
Hot Springs, Virginia
December 5–7, 1977

J. B. LIPPINCOTT COMPANY
PHILADELPHIA • TORONTO



Oral

Dilaudid®

hydromorphone HCl CII

The first step after injectables in post-op analgesia.

Description: Dilaudid is hydromorphone, a hydrogenated ketone of morphine.

Indications: For relief of moderate to severe pain.

Contraindications: Suspected increased intracranial pressure, status asthmaticus.

Warnings: May be habit forming with a potential for addiction equivalent to morphine in equi-analgesic doses. Tolerance may also occur. As with all narcotics, use in early pregnancy only when expected benefits outweigh risks.

Adverse Effects: Nausea, vomiting, diarrhea, constipation, anorexia and somnolence may occur although unlikely with appropriate dose selection.

Dosage and Administration: Dosage must be individualized. The usual adult dose is 2 mg every 4-6 hours, as necessary, for moderate to moderately severe pain. For more severe pain, 3-4 mg or more every 4-6 hours, as necessary, may be required.

Treatment of Overdosage: If overdosage is treated within an hour, emesis and gastric lavage should be attempted. Special attention should be given to respiration and, if depression occurs, it may be antagonized by the use of naloxone hydrochloride (Narcan®)—Endo, nalorphine hydrochloride (Nalline®)—Merck Sharp & Dohme or levallorphan tartrate (Lorfan®)—Roche as recommended by the manufacturer. Other supportive measures should be applied when indicated.

How Supplied: Dilaudid HCl color coded tablets (NOT FOR INJECTION) imprinted with K logo on one side and potency on other side as follows: green—1 mg; orange—2 mg; pink—3 mg and yellow—4 mg. Available in: 1 mg—bottles of 100 (NDC #0044-1021-02), 2 mg—bottles of 100 (NDC #0044-1022-02) and 500 (NDC #0044-1022-03), 3 mg—bottles of 100 (NDC #0044-1023-02), 4 mg—bottles of 100 (NDC #0044-1024-02) and 500 (NDC #0044-1024-03).

Knoll Pharmaceutical Company
Whippany, New Jersey 07981

Member Company, Certified Medical Representative Institute, Inc.

Every day, healthy people leave the hospital—carrying resistant staph.

OF MEDICINE
LIBRARY

Today, more than 80%* of community staph is resistant to penicillin G.

Treat these resistant staph infections as effectively in the office as you do in the hospital.

Prostaphlin®
(oxacillin sodium)

*Ross, S. *et al.*: JAMA *229*: 1075 (Aug. 19) 1974.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Prostaphlin® (oxacillin sodium)
Capsule and Oral Solution (11) PROSTAPHLIN 9/11/75

For complete information, consult Official Package Circular.

Indications: Although the principal indication for oxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to oxacillin sodium should be performed.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of oxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to oxacillin sodium, the physician is advised to continue therapy with a drug other than oxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Oxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A previous hypersensitivity reaction to any penicillin is a contraindication.

Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

The possibility of bacterial and/or fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Experience in premature and newborn infants is limited. Caution should be exercised in administration of the drug to such patients and frequent evaluation of organ system function is recommended.

Safety for use in pregnancy has not been established.

Adverse Reactions: The hypersensitivity reactions reported are skin rashes, urticaria, serum sickness and anaphylactic reactions. Oral lesions such as glossitis and stomatitis have been reported. Fever, eosinophilia, oral and rectal moniliasis have also been reported. Hemolytic anemia, transient neutropenia with evidence of granulocytopenia or thrombocytopenia, neuropathy, and nephrotoxicity (oliguria, albuminuria, hematuria, pyuria, and/or cylindruria) are infrequent and usually associated with high doses of parenteral penicillin.

In some newborns and infants receiving high doses of oxacillin sodium (150 to 175 mg./Kg./day), transient hematuria, albuminuria, and azotemia have been encountered. Although the causal relationship is not entirely clear, infants and newborns treated with high doses of the drug should be observed closely for signs of renal impairment.

One patient developed granulocytopenia while receiving intravenous oxacillin sodium and vancomycin. The blood count returned to normal after both drugs were discontinued. Another patient was reported to have leukopenia during intravenous therapy with oxacillin sodium. These counts were made while the patient was moribund. Thrombophlebitis has occurred in a small percentage of patients after intravenous therapy.

Usual Oral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Administer on empty stomach for maximum absorption.

Usual Parenteral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Children weighing 40 Kg. or more should receive the adult dose.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

Supplied: Capsules—250 and 500 mg. in bottles of 48 and 100. Injectable—250 mg., 500 mg., 1 Gm., 2 Gm., and 4 Gm. dry filled vials for IM/IV use. For Oral Solution—100 ml. bottles, 250 mg./5 ml. when reconstituted.

A.H.F.S. Category 8:12.16

BRISTOL®
BRISTOL LABORATORIES
Division of Bristol-Myers Co.
Syracuse, New York 13201

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

DAVID C. SABISTON, JR., M.D., *Chairman*
Durham, N. C.

J. WESLEY ALEXANDER, M.D.
Cincinnati, O.

WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.

W. GERALD AUSTEN, M.D.
Boston, Mass.

HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.

WARREN H. COLE, M.D.
Asheville, N. C.

MICHAEL E. DE BAKEY, M.D.
Houston, Tex.

STANELY J. DUDRICK, M.D.
Houston, Tex.

J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.

PAUL A. EBERT, M.D.
San Francisco, Calif.

ERIC W. FONKALSRUD, M.D.
Los Angeles, Calif.

FRANK L. A. GERBODE, M.D.
San Francisco, Calif.

FRANK GLENN, M.D.
New York, N. Y.

FRASER N. GURD, M.D.
Ottawa, Canada

OLGA M. JONASSON, M.D.
Chicago, Ill.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.

LEONARD D. MILLER, M.D.
Philadelphia, Pa.

FRANCIS D. MOORE, M.D.
Boston, Mass.

WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.

JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.

JONATHAN E. RHOADS, M.D.
Philadelphia, Pa.

PAUL S. RUSSELL, M.D.
Boston, Mass.

JOHN A. SCHILLING, M.D.
Seattle, Wash.

G. THOMAS SHIRES, M.D.
New York, N. Y.

HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.

DAVID B. SKINNER, M.D.
Chicago, Ill.

FRANK C. SPENCER, M.D.
New York, N. Y.

SAMUEL A. WELLS, JR., M.D.
Durham, N. C.

Emeritus Members

Brian B. Blades, M.D., Washington, D.C., William F. Rienhoff, Jr., Baltimore, Md.
John D. Stewart, M.D., Boca Raton, Fla.

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Second-class postage paid at Philadelphia, Pa., and at additional mailing offices. Published monthly.
Subscription $26.00 per United States. Resident Rate (U.S. only) $19.00.
All other countries $35.00. Single issue $4.00. All prices include postage.

Copyright © 1978 by J. B. Lippincott Co., East Washington Square, Philadelphia, Pa. 19105. Printed in U.S.A.

ANTISEPTIC SECURITY

in scrubbing and prepping

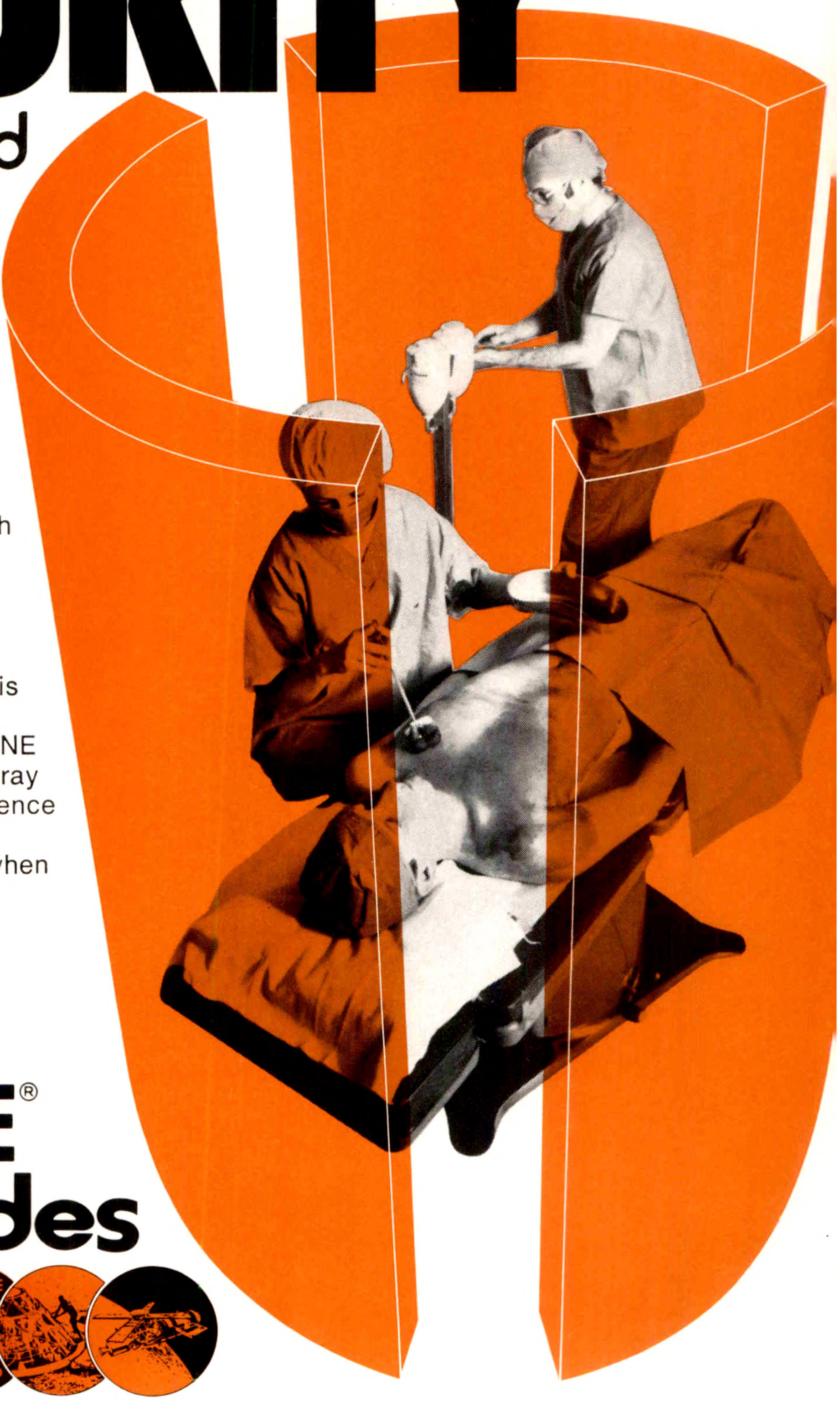
For surgeons, nurses and patients the prompt, broad-spectrum action of BETADINE Microbicides provides topical antiseptic security.

BETADINE Surgical Scrub, for scrubbing by the surgical team and for optimal skin degerming in prepping the patient . . . promptly achieves full microbicidal effect with each usage . . . (in the rare instance of local irritation or sensitivity, discontinue use in the individual).

BETADINE Solution or BETADINE Aerosol Spray, to enhance antisepsis in prepping after initial use of BETADINE Surgical Scrub. BETADINE Solution and BETADINE Aerosol Spray are film-forming . . . active in the presence of blood, pus and serum . . . help maintain postoperative antisepsis when applied to incisions.

Purdue Frederick

© COPYRIGHT 1975, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A7982 165175



BETADINE® Microbicides

Foremost documented
broad-spectrum
topical microbicides

BETADINE Microbicides Chosen by NASA Apollo Skylab

may be implicated in a number of clinical situations, including . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena

Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated.

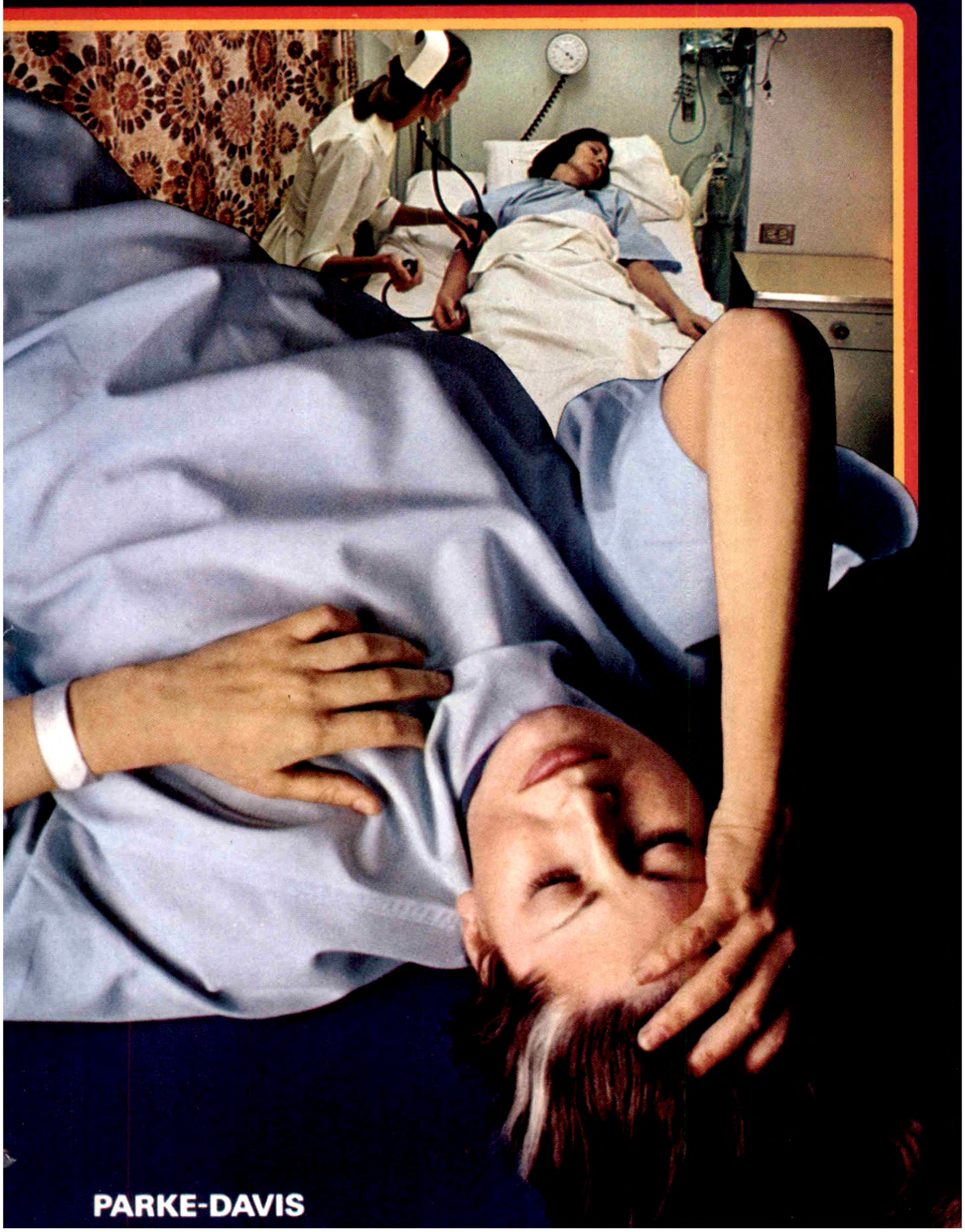
But when bacteroides are implicated, Chloromycetin (chloramphenicol) therapy may well be the conservative course. For, in such situations, the benefits-to-risk ratio with Chloromycetin is very favorable.

See next page for full prescribing information.

Bacteroides...

often an indication for

CHLOROMYCETIN®
(chloramphenicol) Sodium Succinate



PARKE-DAVIS

Prescribing information—Chloromycetin
(chloramphenicol) Sodium Succinate
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae.* It is particularly active against *Salmonella typhi* and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**

   It is not recommended for the routine treatment of the typhoid carrier state.
2. **Serious infections caused by susceptible strains in** accordance with the concepts expressed above.
   - a) *Salmonella* species
   - b) *H influenzae,* specifically meningeal infections
   - c) Rickettsia
   - d) Lymphogranuloma-psittacosis group
   - e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   - f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
  - (1) abdominal distension with or without emesis;
  - (2) progressive pallid cyanosis;
  - (3) vasomotor collapse, frequently accompanied by irregular respiration;
  - (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off RJ

PD-JA-1280-2-P (2-75)

PARKE, DAVIS & COMPANY, Detroit, Michigan 48232

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

ANNALS OF SURGERY

Vol. 187 May 1978 No. 5

CONTENTS

443 **Presidential Address: The War of Regulation (1767–1977)**
H. William Scott, Jr., M.D., *Nashville, Tennessee*

449 **Cardiac Function at Rest and During Exercise in Normals and in Patients with Coronary Heart Disease: Evaluation by Radionuclide Angiocardiography**
Stephen K. Rerych, M.D., *Peter M. Scholz,* M.D., *Glenn E. Newman* M.D., *David C. Sabiston, Jr.,* M.D., *Robert H. Jones,* M.D., *Durham, North Carolina*

465 **Cholecystosonography for the Diagnosis of Cholecystolithiasis**
Peter J. Dempsey, M.D., *Joseph F. Phillips,* M.D., *David L. Warren,* M.D., *Arthur J. Donovan,* M.D., *Mobile, Alabama*

475 **Medical Adrenalectomy with Aminoglutethimide: Clinical Studies in Postmenopausal Patients with Metastatic Breast Carcinoma**
Samuel A. Wells, Jr., M.D., *Richard J. Santen,* M.D., *Allan Lipton,* M.D., *Darrow E. Haagensen, Jr.,* M.D., *Edward J. Ruby,* M.D., *Harold Harvey,* M.D., *William G. Dilley,* PH.D., *Hershey, Pennsylvania*

485 **Staging Laparotomy in Hodgkin's Disease**
William R. Sandusky, M.D., *Robert C. W. Jones, Jr.,* M.D., *J. Shelton Horsley, III,* M.D., *William L. Marsh, Jr.,* M.D., *Thomas W. Tillack,* M.D., *Charles J. Tegtmeyer,* M.D., *Charles E. Hess,* M.D., *Charlottesville, Virginia*

490 **Breast Reconstruction Following Mastectomy for Cancer**
John B. Lynch, M.D., *James J. Madden, Jr.,* M.D., *John D. Franklin,* M.D., *Nashville, Tennessee*

502 **The Prevention of Bypass Enteritis After Jejunoileal Bypass for Morbid Obesity**
T. Brannon Hubbard, Jr., M.D., PH.D., *Baltimore, Maryland*

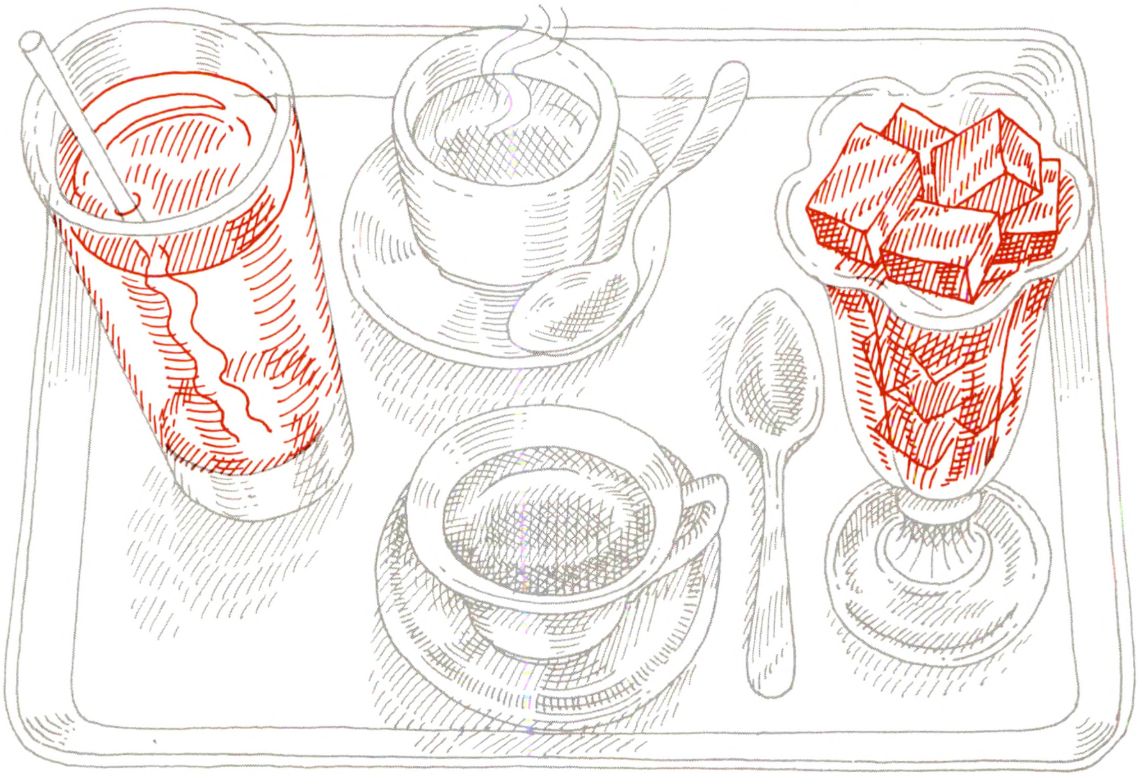
510 **The Comparative Survivals of Alcoholics Versus Nonalcoholics After Distal Splenorenal Shunt**
Robert Zeppa, M.D., *George T. Hensley,* M.D., *Joe U. Levi,* M.D., *Paul R. Bergstresser,* M.D., *Duane G. Hutson, Sr.,* M.D., *Alan S. Livingstone,* M.D., *Eugene R. Schiff,* M.D., *Pat Fink,* R.N., *Miami, Florida*

Starvation diet?

Standard clear liquid regimen: 400 kcal daily—trace protein

Not when you fortify with Vivonex® HN!

Clear liquid regimen fortified with 5 packets Vivonex HN:
1,900 kcal, 10 gm nitrogen (62.5 gm protein) daily

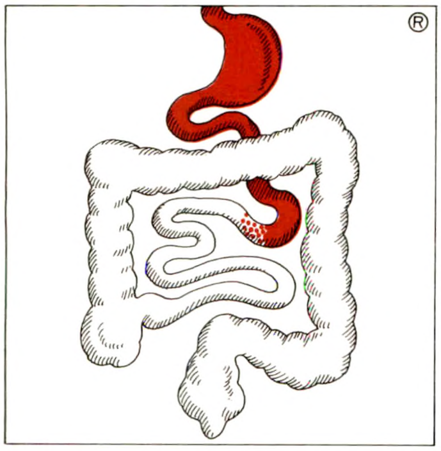


For the nutritional management of protein-calorie malnutrition...Vivonex HN

The usual clear liquid regimen provides only 400 calories daily, with only trace protein. The addition of Vivonex HN to the regimen can add substantial amounts of vital protein and calories for the nutritional management of protein-calorie malnutrition. Vivonex HN is readily accepted by patients on clear liquid regimens when mixed into gelatin desserts, or when served as a beverage in the various flavors now available with Vivonex Flavor Packets.

Because Vivonex HN is formulated with free amino acids, simple carbohydrate and low fat, it requires virtually no active digestion and is absorbed almost completely with negligible residue. Thus it supports the diet objective.

Add Vivonex HN to conventional clear liquids before and after surgery, and when clean-bowel preparation is necessary before surgery or diagnostic procedures. Vivonex HN is also valuable as an enteral alternative to parenteral feeding, as an adjunct to routine parenteral glucose and fluids, and for patients with GI disorders.



Protein-calorie fortification... negligible residue

Vivonex® HN HIGH NITROGEN SOLUBLE POWDER

free amino acid...complete enteral nutrition
minimal digestion...maximal absorption

Supplied unflavored in boxes containing ten 80-gram packets. Each packet provides 300 kcal, 2 gm usable nitrogen (12.5 gm usable protein), as well as carbohydrate, fat, essential vitamins and minerals.

Flavor with Vivonex Flavor Packets
(artificially flavored) Orange, strawberry, grape, beef broth, and tomato. *Also available:* Vivonex Standard Diet. Supplied unflavored in boxes containing six 80-gram packets. Each packet provides 300 kcal. Six packets provide 1,800 kcal, 5.88 gm usable nitrogen (36.75 gm usable protein).

Please note: Information on Vivonex usage and precautions accompanies the product and should be reviewed before use.

® **Originators of chemically defined diets**
EATON LABORATORIES
division of Morton-Norwich Products, Inc.
Norwich, New York 13815

CONTENTS *Continued*

515 Results of Interposition "H" Grafts for Portal Hypertension
Bernard W. Thompson, M.D., F.A.C.S., *Robert E. Casali,* M.D., *Raymond C. Read,* M.D., F.A.C.S., *Gilbert S. Campbell,* M.D., F.A.C.S., *Little Rock, Arkansas*

523 Ten Years Experience with Intravenous Hyperalimentation and Inflammatory Bowel Disease
James L. Mullen, M.D., *W. Clark Hargrove,* M.D., *Stanley J. Dudrick,* M.D., *William T. Fitts, Jr.,* M.D., *Ernest F. Rosato,* M.D., *Philadelphia, Pennsylvania*

530 Comparison of the Results of Resection, Bypass, and Bypass with Exclusion for Ileocecal Crohn's Disease
William P. Homan, M.D., *Peter Dineen,* M.D., *New York, New York*

536 The Surgical Aspects of Chronic Mucosal Inflammatory Bowel Disease (Chronic Ulcerative Colitis)
Jonathan A. Van Heerden, M.B., F.R.C.S(C), *Donald C. McIlrath,* M.D., *Martin A. Adson,* M.D., *Rochester, Minnesota*

542 Urinary Tract Complications with Rectal Surgery
John R. Beahrs, M.D., *Oliver H. Beahrs,* M.D., *Margaret M. Beahrs,* M.D., *Frank J. Leary,* M.D., *Rochester, Minnesota*

549 Reassessment of Intraoperative Decisions: Why Operations for Cancer of the Large Bowel Fail
Carl O. Knutson, M.D., *Donald E. Fry,* M.D., *Ronald D. Barbie,* M.D., *Hiram C. Polk,* M.D., *Louisville, Kentucky*

555 Management of Pancreatic Trauma
Ronald C. Jones, M.D., *Dallas, Texas*

565 The Role of Peritoneal Lavage in Severe Acute Pancreatitis
John H. C. Ranson, M.D., *Frank C. Spencer,* M.D., *New York, New York*

576 Results of Elective Duodenal Ulcer Surgery in Women: Comparison of Truncal Vagotomy and Antrectomy, Gastric Selective Vagotomy and Pyloroplasty, Proximal Gastric Vagotomy
J. Lynwood Herrington, Jr., M.D., *John L. Sawyers,* M.D., *Nashville, Tennessee*

- **Compact...**easy to store...all in a sealed, plastic container
- **Versatile...**easily snaps onto the top of a magnesium citrate bottle...can be used with other saline cathartics or with castor oil
- **Economical...**suggested retail price is less than most other kits
- **Convenient...**for nursing staff or the outpatient. Sold in a handy dispenser of 5.

With the Dulcolax Bowel Prep Kit plus magnesium citrate "...the reexamination rate of patients because of poorly cleansed colons has fallen to approximately 1 percent of all barium enema studies."[1]

[1] Sorrentino A P et al. Am J Hosp Pharm *26*:432-435, 1969.

Boehringer Ingelheim Ltd.
Ridgefield, CT 06877

Each kit contains:

4 Dulcolax tablets of 5 mg bisacodyl

complete patient instructions

1 Dulcolax suppository of 10 mg bisacodyl

Announcing the New Dulcolax® Bowel Prep Kit

AMICAR®

AMINOCAPROIC ACID

INTRAVENOUS • TABLETS • SYRUP

INDICATIONS: AMICAR has proved useful, in many instances, in the treatment of excessive bleeding which results from *systemic hyperfibrinolysis* and *urinary fibrinolysis*. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Systemic hyperfibrinolysis, a pathological condition, may frequently be associated with *surgical complications* following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; *hematological disorders* such as aplastic anemia, *abruptio placentae, hepatic cirrhosis, neoplastic disease* such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is *surgical hematuria* (following prostatectomy and nephrectomy) or *non-surgical hematuria* (accompanying polycystic or neoplastic diseases of the genitourinary system).

CONTRAINDICATIONS: AMICAR should not be used when there is evidence of an active intravascular clotting process.

WARNINGS: Safe use of AMICAR has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of child-bearing potential and particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible hazards.

PRECAUTIONS: AMICAR *aminocaproic acid* has a very specific action in that it inhibits both plasminogen activator substances and, to a lesser degree, plasmin activity. The drug should NOT be administered without a definite diagnosis, and/or laboratory findings indicative of hyperfibrinolysis (hyperplasminemia).*

*Stefanini, M. and Dameshek, W. The Hemorrhagic Disorders, Ed. 2, New York, Grune and Stratton, pp. 510-514, 1962.

The use of AMICAR should be accompanied by tests designed to determine the amount of fibrinolysis present. There are presently available (a) general tests, such as those for the determination of the lysis of a clot of blood or plasma and (b) more specific tests for the study of various phases of fibrinolytic mechanisms. These latter tests include both semiquantitative and quantitative technics for the determination of profibrinolysin, fibrinolysin, and antifibrinolysin.

Animal experiments indicate particular caution should be taken in administering AMICAR to patients with cardiac, hepatic or renal diseases.

Demonstrable animal pathology in some cases have shown endocardial hemorrhages and myocardial fat degeneration. The use of this drug should thus be restricted to patients in whom the benefit hoped for would outweigh the hazard. Physicians are cautioned in the use of this product because of animal data showing rat teratogenicity and kidney concretions.

Rapid intravenous administration of the drug should be avoided since this may induce hypotension, bradycardia and/or arrhythmia.

One case of *cardiac* and *hepatic lesions* observed in man has been reported. The patient received 2 grams of aminocaproic acid every 6 hours for a total dose of 26 grams. Death was due to continued cerebral vascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

If it is accepted that fibrinolysis is a normal process, potentially active at all times to ensure the fluidity of blood, then it must also be accepted that inhibition of fibrinolysis by aminocaproic acid *may* result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of *intravascular clotting* which followed this treatment. Rather, it appears that such intravascular clotting was most likely a result of the fibrinolytic disease being treated.

It has been postulated that *extravascular clots* formed *in vivo* with incorporated aminocaproic acid may not undergo spontaneous lysis as do normal clots. However, it is the consensus of experts that the few reported cases of extravascular clotting could have occurred in the absence of aminocaproic acid treatment.

ADVERSE REACTIONS: Occasionally nausea, cramps, diarrhea, dizziness, tinnitus, malaise, conjunctival suffusion, nasal stuffiness, headache, and skin rash have been reported as results of the administration of aminocaproic acid. Only rarely has it been necessary to discontinue or reduce medication because of one or more of these effects.

Thrombophlebitis, a possibility with all intravenous therapy, should be guarded against by strict attention to the proper insertion of the needle and the fixing of its position.

DOSAGE AND ADMINISTRATION: *INITIAL THERAPY*—An initial priming dose of 5 grams of AMICAR administered either orally or intravenously followed by 1 to 1¼ gram doses at hourly intervals thereafter should achieve and sustain plasma levels of 0.130 mg./ml. of the drug. This is the concentration apparently necessary for the inhibition of systemic hyperfibrinolysis. Administration of more than 30 grams in any 24-hour period is not recommended.

INTRAVENOUS: AMICAR *aminocaproic acid* intravenous is administered by infusion, utilizing the usual compatible intravenous vehicles (e.g. Sterile Water for Injection, physiologic saline, 5% dextrose or Ringer's Solution). RAPID INJECTION OF AMICAR INTRAVENOUS UNDILUTED INTO A VEIN IS NOT RECOMMENDED.

For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 16 to 20 cc. (4 to 5 grams) of AMICAR intravenous be administered by infusion during the first hour of treatment, followed by a continuing infusion at the rate of 4 cc. (1.0 gram) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

ORAL THERAPY: If the patient is able to take medication by mouth, an identical dosage regimen may be followed by administering AMICAR Tablets or 25% Syrup as follows: For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 10 tablets (5 grams) or 4 teaspoonfuls of syrup (5 grams) of AMICAR be administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 gram) or 1 teaspoonful of syrup (1¼ grams) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

REV. 7/72

LEDERLE LABORATORIES

GENERAL SURGEON

The East Tennessee State University Department of Surgery invites applications from, and nomination of general surgeons.

Preference will be given individuals with special interest and experience in Laboratory research.

Certification by the American Board of Surgery is required for the position.

Letters of nomination or applications, along with a current curriculum vitae, should be sent before June 15, 1978 to:

Lester R. Bryant, M.D.
Chairman
Department of Surgery
ETSU College of Medicine
Johnson City, Tennessee 37601

ETSU is an Equal Opportunity/Affirmative Action Employer.

FACULTY POSITION OPEN

College of Medicine, King Faisal University Dammam, Saudi Arabia

PROFESSOR AND CHAIRMAN, DEPARTMENT OF SURGERY

Applications are invited from U.S., British and Canadian surgeons with at least ten years teaching experience in a medical school. Opening is for September 1978; interviews scheduled with the Dean in the United States early in 1978. Language of instruction is English.

Salary and Benefits:

Academic Salary monthly in Saudi Riyals (SR)	+ *Clinical Bonus of 50%*	= *Total approximate* *annually in* U.S. dollars
SR 10,000	SR 5,000	$50,000

Free furnished accommodations and annual leave with travel allowance to country of origin for family of four. No Saudi income tax.

Send curriculum and references with addresses and telephone numbers to:

Mohammed T. Altorki, M.D., MRCP
Dean of the Medical Faculty
King Faisal University
c/o Saudi Arabian Educational Mission
2223 West Loop South, Suite 400
Houston, Texas 77027

Specify dates of teaching appointments and availability.

Notice to Contributors and Subscribers

ANNALS OF SURGERY is a monthly journal which considers for publication original articles in the field of surgery. It is the oldest continuously published journal in the English language solely devoted to the surgical sciences. The Editorial Board considers only papers judged to offer significant contributions to the advancement of surgical knowledge.

CONTRIBUTIONS. Four typed copies of the manuscript and four copies of the illustrations should be sent prepaid to the Chairman of the Editorial Board of ANNALS OF SURGERY:

David C. Sabiston, Jr., M.D.
Annals of Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

Manuscripts and references should be typed double spaced on one side of 8½ × 11 paper leaving wide margins. Authors should retain a complete copy of the manuscript including illustrations in the event that the manuscripts are lost in the mail. A complete address for reprint requests should be included on the title page together with the name of the institution from which the work is being published.

An abstract of *not more than 200 words* should be placed at the beginning of the manuscript. It should accurately reflect the paper and provide readers with a reliable impression of the contents and conclusions of the work.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement should be expressed in the metric system. Temperature should be expressed in degrees centigrade. All contributions should be submitted in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Color illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink or transfer lettering, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

An alphabetical list of numbered references should appear at the end of the manuscript with corresponding numbers in the text. All references should be specifically mentioned in the body of the manuscript. The list of references should be *selective* with not more than 20 references except under unusual circumstances. References should conform to the style of the Index Medicus.

McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., 174:58, 1971.

PUBLISHER'S NOTICES

CHANGE OF ADDRESS: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

BUSINESS ADDRESS: Subscriptions, reprints, advertising, and all business communications should be addressed to:

ANNALS OF SURGERY
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $25.00 per year in United States and possessions; all other countries $34.00. All prices include postage. Single issues $4.00. Rate for Residents, U.S. only, $19.00.

The publishers accept no responsibility for opinions expressed by contributors.

For Professionals Only

pHisoHex effectively reduces skin levels of resident gram-positive bacteria—including staph. With a longer duration of action than any iodophor.

When pHisoHex is used regularly, a bacteriostatic film accumulates and usually won't wash away for days. Rinse thoroughly after use, but not with alcohol.

pHisoHex. Because professional people need a professional wash and scrub.

CLINICAL PHARMACOLOGY: pHisoHex is a bacteriostatic cleansing agent. It cleanses the skin thoroughly and has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use. This antibacterial residue is resistant to removal by many solvents, soaps, and detergents for several days.

pHisoHex has the same slight acidity as normal skin (pH value 5.0 to 6.0).

INDICATIONS AND USAGE: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

CONTRAINDICATIONS: pHisoHex should not be used on burned or denuded skin.

It should not be used as an occlusive dressing, wet pack, or lotion.

It should not be used routinely for prophylactic total body bathing.

It should not be used as a vaginal pack or tampon, or on any mucous membranes.

pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

WARNINGS: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Rapid absorption of hexachlorophene may occur with resultant toxic blood levels, when preparations containing hexachlorophene are applied to skin lesions such as ichthyosis congenita, the dermatitis of Letterer-Siwe's syndrome, or other generalized dermatological conditions. Application to burns has also produced neurotoxicity and death.

pHisoHex SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

Infants have developed dermatitis, irritability, generalized clonic muscular contractions and decerebrate rigidity following application of a 6 per cent hexachlorophene powder. Examination of brainstems of those infants revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3 per cent hexachlorophene. Moreover, a study of histologic sections of premature infants who died of unrelated causes has shown a positive correlation between hexachlorophene baths and lesions in white matter of brains.

pHisoHex is intended for **external use only.** If swallowed, pHisoHex is harmful, especially to infants and children. **pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.**

PRECAUTION: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly with water.

ADVERSE REACTIONS: Adverse reactions to pHisoHex may include dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

TREATMENT OF ACCIDENTAL INGESTION: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities.

If patients are seen early, the stomach should be evacuated by emesis or gastric lavage. Olive oil or vegetable oil (60 ml or 2 fl oz) may then be given to delay absorption of hexachlorophene, followed by a saline cathartic to hasten removal. Treatment is symptomatic and supportive; intravenous fluids (5% dextrose in physiologic saline solution) may be given for dehydration. Any other electrolyte derangement should be corrected. If marked hypotension occurs, vasopressor therapy is indicated. Use of opiates may be considered if gastrointestinal symptoms (cramping, diarrhea) are severe. Scheduled medical or surgical procedures should be postponed until the patient's condition has been evaluated and stabilized.

HOW SUPPLIED: pHisoHex is available in unbreakable plastic squeeze bottles of 5 oz (refillable) and 1 pt, and in plastic bottles of 1 gal.

Also available—¼ oz (8 ml) unit packets, boxes of 50.

pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts. A special type of stainless steel must be used or undesirable discoloration of the product or oxidation of metal may occur. Specially designed dispensers for hospital or office use may be obtained through your local dealer.

pHisoHex®
brand of
hexachlorophene
detergent cleanser

contains a colloidal dispersion of hexachlorophene 3% (w/w) in a stable emulsion consisting of entsufon sodium, petrolatum, lanolin cholesterols, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH is adjusted with hydrochloric acid. Entsufon sodium is a synthetic detergent (sodium octylphenoxyethoxyethyl ether sufonate).

Winthrop Winthrop Laboratories, New York, NY 10016

3084

ANNALS OF SURGERY

Vol. 187 May 1978 No. 5

Presidential Address:

The War of Regulation (1767–1977)

H. WILLIAM SCOTT, JR., M.D.

From the Department of Surgery,
Section of Surgical Sciences,
Vanderbilt University Medical Center,
Nashville, Tennessee

PLEASE ACCEPT MY SINCERE gratitude for the great honor you have granted me to serve as your President during this year. While many of you are more deserving of this honor than I, there can be no one among you who is more enthusiastic about holding this high office and no one who is more reluctant to leave it! I keep wondering if in some way I can be recycled.

Presidential addresses presented to this association have frequently described works of men and historic events that have been a part of the rich heritage of the South. In this tradition I want to talk to you today about the War of the Regulation—firstly, a war that was waged from 1767 to 1771 by American colonial citizens against their government and which the colonists lost. Secondly, I want to discuss with you a War of the Regulation which the American government is waging in 1977 against its citizens and which the citizens are in grave danger of losing.

Let me begin by directing your attention to colonial North Carolina during the latter half of the eighteenth century. More specifically, let us look at the county of Orange near the center of the Royal Province with the town of Hillsborough, founded in 1754, as its county seat.

At that time the colonial settlers, largely of English origin, were concentrated along the eastern seaboard. The seat of the Royal Provincial government was the eastern town of New Bern, founded by Swiss colonists in 1710 and selected by British Governor William Tryon in 1766 to be the site of his palatial residence. Orange County, named after the Dutch Prince of Orange who became King William III of England, was frontier country, settled largely by German and Scotch-Irish colonists. The latter designation was given to those descendants of lowland Scots and "borderers" who had originally emigrated from Scotland to the Ulster plantations of Northern Ireland in the seventeenth century and whose families subsequently emigrated to the American colonies by the hundreds in the early eighteenth century—some historians say to escape the long sermons of their own Presbyterian ministers. At best these emigré Scots had little enthusiasm for English rule.

During the decade just before the Revolutionary War, there was a great deal of restless discontent among the colonists in what was then called the "back country" in North Carolina. The principal causes were the inept colonial policies of the British crown, the tyrannical measures of Royal Governor Tryon and the corrupt governmental administration of Edmund Fanning, Tryon's representative in Hillsborough.

Fanning was a native of New York and a Yale graduate who came to Hillsborough in 1762. He soon became Register of Deeds of Orange County and, subsequently, Justice of the Peace and Governor Tryon's factotum in the frontier capitol. His corrupt practices and harsh measures enraged the colonists. Embezzlement of tax money by the 11 sheriffs on Fanning's staff was further cause for outrage. In a widespread movement to rebel against the corrupt county governments in 1767 the colonists in Orange and surrounding

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

0003-4932-78-0500-0443-0075 © J. B. Lippincott Company

counties organized themselves into a group known as the Regulators.

At its beginning the Regulators' movement was enveloped in secrecy with the objective of establishing good local government. Efforts to obtain justice in local county courts failed consistently. When the Regulators appealed for justice to the Assembly at New Bern, Governor Tryon had the Assembly dissolved. By 1770 the spirit of the Regulation was widely aroused and local officials in many counties were openly accused of dishonesty, extortion and bribery by the Regulators. In September, 1770 in Hillsborough 150 Regulators took over Judge Richard Henderson's courtroom, pulled Edmund Fanning from behind the judge's bench and gave him a public whipping. For two days there was rioting and destruction of much governmental property and court records. The violence caused a special session of the Assembly to be convened in New Bern that began at once to draw up reform measures in line with the demands of the Regulators, providing for honest dealing by the sheriffs, attorneys and court officers and specifying their fees. However, when rumor reached the Assembly that the Regulators were going to march on New Bern, the reform measures were replaced by punitive legislation. The Attorney General was instructed to prosecute charges of riot in any superior court in the province. All who avoided the summons of the court for 60 days were to be declared outlaws and were to be shot on sight by the militia.

The Regulators were quick to retaliate. They announced that they would pay no more taxes, that no more court sessions were to be held and that Edmund Fanning and any other officials or attorneys who came among them were to be killed.

Governor Tryon ordered a superior court session to be held in Hillsborough in March, 1771. To quell anticipated riots, Tryon raised a force of militia in the eastern counties by offering a bounty of 40 shillings per man and began the long march to Hillsborough with over 1000 men. Tryon's men were well armed and had plenty of ammunition. They encamped outside Hillsborough in May, 1771 and were joined by an Orange County militia company headed by Fanning. This raised Tryon's numbers to about 1450 men. This well armed force met an ill-equipped, poorly organized band of about 2000 Regulators at Great Alamance creek in Orange County on May 16, 1771 and after a two hour battle Tryon's force gave the Regulators a crushing defeat. Tryon's losses were nine men killed and 61 wounded. The Regulators lost nine men killed and over 200 wounded.

Tryon took 15 Regulators prisoner. One of these, James Few, was immediately hanged on the battlefield and subsequently 12 others were judged guilty of treason; six of these were hanged and six were later pardoned by King George III.

On the day after the battle of Alamance, Tryon proclaimed pardon for all those suspected Regulators who would take an oath of allegiance to the crown, excepting the captured and those whom he outlawed. In the end about six thousand men took the oath. Some 1500 people, however, left the Royal Province of North Carolina and emigrated westward.

The Regulation movement in North Carolina failed in 1771 to eliminate corruption in local colonial government but it showed that the frontier counties were rebellious against a form of government in which the people could not hold officials accountable for their conduct in office. In this historic vignette we can clearly recognize the spirit, shared by a majority in all colonies, which subsequently led to the American Revolution against the British crown and to the adoption of a constitution for the United States based on government by and for the people who are governed.

From this historic springboard, let me invite you to take a quantum leap in time from the War of the Regulation in the eighteenth century to our current situation in 1977. More specifically, let us look at the relations between today's huge federal government and one segment of those who are governed, the medical and scientific community.

In my view of the scene today, I am persuaded that the War of the Regulation has been resumed, but the lines of battle have been redrawn and the role of the contestants strangely reversed!

The Regulators in the war that is waged today no longer wear the white hats with which we adorn our pioneer ancestors; rather in our current imagery a vast army of the federal establishment with a predilection to wear black hats represents the Regulators of 1977. To carry this conceit further, the malevolent spirit of British Governor Tryon that harassed North Carolina colonists over 200 years ago seems to have surfaced in the late Twentieth Century to harass physicians, surgeons and hospitals in the power structure of our own federal government—the great medical regulator of today!

Our federal government first entered the regulatory field in 1887 with the creation of the Interstate Commerce Commission (ICC) which was organized to crack down on the railroad barons of that day. In 1920 Congress authorized the ICC to set both minimal and maximal rates for railroads. Some observers view this as the beginning of the unfair practices of federal regulatory agencies in stifling competition and protection of the business which they regulate.

Forty-five years ago President Franklin Roosevelt invoked the massive power of the federal government for social action and economic control. With the multiple programs of the "new deal" came the socialistic ideas of the primacy and benevolence of big, centralized government and its role in the solutions of the nation's problems. Since Roosevelt's time these concepts, bordering on national socialism, have been upheld by the liberal establishment in Congress, in the federal bureaucracy, and by the liberal media of our country. These socialistic trends flourished under Presidents Kennedy and Johnson, and with the flowering of multiple, costly federal programs came a flood of federal agencies established by Congress to administer and regulate them. The most massive expansion has occurred in the fields of health, welfare and environmental control. Over the last decade the government's alphabet soup has had OSHA, EPA, CPSC, ERDA, FEC, FEA and EEOC added to ICC, FDA, FCC, FPC, CAB, SEC and FTC.

During the 1970's, state governments and private industries, including the health care industry which may be the most heavily regulated of all industries, have become deluged by the ceaseless flow of complex, arbitrary, unnecessary, unclear and frequently unrealistic rules and regulations imposed by the federal government. The General Services Administration calculates that government forms alone cost the private sector 20 billion dollars annually and the government another 20 billion dollars to read them.

Phillips and Sprague in a report to the American Hospital Association consider that the proliferation of regulations, especially for hospitals, has reached a critical mass with bureaucratic inertia too heavy to control. The proliferation of health care legislation during the 1970's has been accompanied by complex and highly integrated sets of social and economic regulation. In addition, the methods for enforcing regulations have increased and include institutional licensure and accreditation, franchising, stipulations on loans and grants, interest subsidy, institutional tax exemptions, personnel licensure and certification, drug and device licensure, private drug evaluation and listing, professional liability, fines, administrative orders and public disclosure.

As Phillips and Sprague point out, "regulations can be classified by their purpose: economic regulation of prices, rates or fees to affect conditions in the market and social regulation of services and practices to affect conditions regarding individual rights and public health and welfare." However, the overlapping of regulatory activity by multiple federal agencies and their separate, often disparate and even paradoxical standards and rules have created a nightmare for the health care industry and particularly for hospitals.

Undoubtedly, the most complex, confusing and rapidly changing group of regulations involving hospitals has to do with codes and standards associated with design, construction and maintenance of facilities. In the past, the regulation of hospital construction through national standards implemented at state level to ensure the safety of patients has always been an accepted responsibility shared by government and hospitals. However, in the last decade Congress has acted to incorporate these standards into the bodies of legislation having to do with patient care and complicated by formulas for reimbursement of services.

The standards and codes are changed in an almost ceaseless fashion. In one recent year according to Phillips and Sprague, there were 4800 pages of changes in the total National Fire Protection Association (NFPA) standards, 600 pages in Building Officials and Administrators Code and 500 in the Uniform Building Code.

Leonard Cronkhite, President of Boston Children's Hospital, commenting on the plight of hospitals in his Chairman's Address to the Association of American Medical Colleges said last year, "I doubt that any one of us could, even with unlimited funds, comply with this bureaucratic lunacy short of hiring a permanent construction crew to renovate on a year round basis." Cronkhite also made the sage observation that the enormous bureaucratic structure of the federal government in terms of its growth rate and invasiveness has many of the characteristics of a malignancy.

The major objectives behind the massive intrusion of the federal government into the regulation of health care institutions and medical practice have had to do ostensibly with public safety and with control of the costs of medical care. There can be no quarrel with the soundness of these objectives. They are and have been long supported by the private sector. However, as so pleasantly stated by HEW Secretary Califano to the AMA Convention last summer, it is the federal government's view that the health care industry has not only failed to contain costs of medical and hospital care, but has been largely responsible for the recent inflationary rises in costs. According to Califano not only is health care spending eating up an ever larger portion of the gross national product, but it is his prediction that by 1980 total health expenditures in the United States will double and, if unchecked, total hospital costs could reach 220 billion dollars by 1985.

However, Secretary Califano testified before Congress in November, 1977 that HEW loses more than $2 billion per year in fraud, over-payments and other bureaucratic snafus. Losses were said to result from massive over-payments to ineligible recipients, from fraudulent claims by clients, from abuse by doctors, pharmacists and other health care providers and from failure to collect more than $600 million from third party insurers. This testimony prompted a Chicago Tribune editorial on November 10 which is most pertinent, "It is difficult—perhaps impossible—to eliminate all waste and fraudulent loss when bureaucrats run such large scale programs as Medicaid. But that annual $2 billion waste in one program alone should flash an oversized red light at government officials and legislators pushing national health insurance plans. Until HEW proves to Congress it can run Medicaid without losses amounting to seven percent of total spending, it would be foolish, and intolerably expensive, to expand such services."

The federal establishment appears to presume that within the medical and scientific community there are large numbers of ignorant evil-doers, chiefly surgeons, who will, if not watched closely, violate the civil rights of their patients, steadfastly refuse to provide them with primary care, mental health, and preventive medicine, treat them with drugs which cause cancer in federal rats, fail to obtain a second opinion, and without informed consent submit them to unnecessary surgery for which a fraudulent claim is made against Medicare for a fee of over $100,000.

These erroneous presumptions, ridiculous in the extreme, have apparently been responsible for the increased rigidity of the Food and Drug Administration, HEW's restrictions on clinical investigation, the informed consent controversy, the concept of mandatory second opinions for elective surgery, altered commitment procedures for the mentally ill and retrospective audits of all aspects of medical care in hospitals as measured by federally approved norms. Containment of costs of the Medicare and Medicaid programs is the true objective of the Professional Standards Review Organization, although the government insists that enhancement of the quality of medical care is the aim of PSRO.

The War of the Regulation against our profession and our hospitals has been enthusiastically supported and applauded with Naderesque zeal by the liberal media who respect and love us dearly, about as much as does Secretary Califano.

Why is this War of the Regulation being waged against us by our federal establishment at a time when the United States of America has a superb pluralistic health care delivery system based on free enterprise in the private sector with voluntary self-regulation—a system that is outstandingly superior to that of any other country in the world today?

In attempting to answer this question, let us agree initially that codes, standards and regulations are clearly necessary in the health care field. Traditionally, these have been developed and administered by state and local governments in collaboration with voluntary agencies of the private sector such as the Joint Commission on Accreditation of Hospitals. However, the recent study of regulation made by the Hospital Association of New York State identified a total of 164 different agencies with some jurisdiction over hospitals in New York State: 96 at state level, 40 at federal, 18 city-county and ten voluntary agencies. The study indicated that the majority of these regulatory bodies are concerned with bureaucratic matters having little to do with patient care but much to do with administrative, financial and informational services. This overgrown regulatory system in New York has become a costly, counterproductive burden which increases the cost of health care. Clearly, the zeal for over-regulation has become rampant at the state level.

The high command in the War of the Regulation today, however, is the enormous federal bureaucracy. As Leonard Cronkhite has observed, this is a "loose federation of single purpose agencies, bureaus, commissions, and boards so highly compartmentalized as to be unmanageable. Each agency pursues its single purpose zealously without regard for any possible aggregate national purpose—bureaucracy has much more autonomy than any other branch of government. Using the loose mandate from Congress that the various secretaries shall promulgate regulations to implement a given law, the regulations themselves become, in effect, the law."

Although on legal grounds only state governments, not agencies of the federal government can regulate health care markets directly, the federal government does in fact regulate those markets through the exercise of its power of the purse. In providing grants to states the federal government characteristically places regulatory requirements on them. The strictness of requirements depends on a mixture of congressional and federal bureaucratic objectives.

John T. Dunlop, former Secretary of Labor, thinks that a major reason for the attraction of regulatory legislation in recent years has been the belief that regulation is a speedy, simple and cheap procedure. "Perhaps, too," he says, "because the majority of congressmen are lawyers, and not business executives, labor leaders, economists or labor mediators, they are apt to think of social and economic problems in legal terms. For these and other reasons, when a problem acquires national concern . . . the natural reaction has been to create a new regulatory agency to deal with it."

Two years ago, Theodore Cooper pointed out the stark fact that the tremendous increase in governmental expenditures in the health field greatly increases the ability—"some would say the obligation—of the federal government to impose its will on every segment of the health establishment. . . . It is a small jump from the provision of money to the imposition of control. As we have seen all too often once that jump is made, it is virtually never reversed."

Former Secretary for Health, Charles C. Edwards, argues that our present health care system with its rising, inflated costs is headed for certain financial collapse with the inevitable result of total federal takeover and control of all medical services and facilities. His suggestion is that a strong centralized National Health Authority be established to create national regulations on an aggregate rather than a piecemeal basis for the entire health care industry. Edwards stipulates that this is a mandatory step, if the chaotic alternative is to be avoided, before initiation of national health insurance which he strongly favors. Without such regulation he believes that the adoption of national health insurance would hasten rather than prevent the collapse of the system.

Perhaps another major cause of the massive governmental regulatory attack on the health care industry that might be considered by paranoid surgeons and other observers of the current national scene is the possibility of a diabolical plot by evil bureaucrats aimed at the destruction of the voluntary, free-enterprise portion of our pluralistic American system of health care and its replacement by a totalitarian socialistic system of governmental control. The George Orwell concept of "double think" as used in his terrifying book *1984* may be implicated in the overwhelming likelihood that overregulation of the health care industry under the rubric of cost containment will most certainly have the diametrically opposite effect and actually increase the costs of health care. *1984* may be closer than we think!

That these thoughts may be something more than paranoid surgical delusions is signalled by the activities of the federal health care planners during the last few years. There are ten health policies listed in Section 1802 of the National Health Planning and Resources Development Act. They are to be used by the National Council on Health Planning and Development and the Secretary of HEW in formulating national health goals and by Health Systems Agencies and State Health Planning and Development Agencies in developing and carrying out their plans and programs. Since these priorities on health policies were introduced into Congress in 1973 they are in no way new. They are linked to the three overall purposes of Public Law 93-641 which are: equal access to health care, improved quality of care and cost constraint.

Priority 1 addresses the need to provide primary health care to the underserved. Priority 2 is concerned with multi-institutional systems for coordinating or consolidating health services and Priority 7 with the development of appropriate levels of care within geographical areas. Priority 3 calls for the development of medical group practices and other organized systems of health care (this is the concern of the Health Maintenance Organization Act of 1973). Priority 4 calls for the training and increased utilization of physician assistants and especially nurse clinicians. Priority 5 encourages the development of multi-institutional arrangements for shared support services. Priority 6 calls for promotion of activities to achieve improvements in the quality of health services such as needs identified by the activities of PSROs. Priority 8 concerns itself with prevention of disease, with nutrition and the environment. Priority 9 calls for uniform cost accounting, reimbursement procedure and utilization reporting. Priority 10 asks for the development of more effective health education and promotion.

At first glance these policies seem quite benevolent, but their progressive implementation by the federal government has generated a proliferation of regulations and bureaucracy that suggest strongly a movement toward total governmental control of health care. The Kennedy-Corman bill, if passed by Congress, would promptly establish national socialistic control of health care in the USA, but, happily, there appears to be little Congressional support for it.

Currently, the Carter administration is urging Congress to pass the Hospital Cost Containment Act of 1977 as a necessary prelude to the administration's anticipated proposal for national health insurance. The various bills in the Congressional hopper which propose national health insurance represent to paranoid surgeons merely additional invitations for more massive inflationary governmental expenditures in health care, huge increases in the federal bureaucracy, and major escalation of the War of the Regulation which will lead us further down the skids to socialized medicine.

What can we do about these terrifying implications of the current phase of the War of the Regulation?

Since lawyers produce most of the bureaucratic regulations, the initial response of a paranoid surgeon might echo Shakespeare's character Dick the Butcher in King Henry VI, Part 2, who said, "The first thing we do, let's kill all the lawyers."

On more mature reflection, however, that solution, no matter how attractive it may be to some of you, is not practical—lawyers greatly outnumber us and, furthermore, they have made a law against Dick the Butcher's suggestion.

A second solution to this War of the Regulation that might come to the mind of a paranoid southern surgeon is to march to the banks of the Potomac and lay siege to the Department of HEW. Again, this solution is not practical. The bureaucrats also greatly outnumber us and I am sure that a siege would be against HEW's regulations. Besides, when southerners marched up in that area some years ago, they ran into a lot of hostility, especially in the vicinity of a place named Gettysburg.

In a more serious vein, we should be aware of and commend the activities of the American Hospital Association in its approach to the problems of bureaucratic over-regulation. The AHA has in recent years pressed to obtain adequate representation on code and standard writing bodies which affect hospitals and AHA member institutions are now said to have the opportunity to take responsive action with regard to both current and proposed health care standards. The AHA has started a research and data collection program to assess safety hazards and thus to identify the need for standards before one is actually developed.

Several states have initiated action more directly related to the federal regulatory process. For example, Kentucky has amended its regulatory statutes to prohibit conflicting federal and state standards and unnecessary and duplicative inspections by federal, state and local agencies. Clearly, more state action is needed.

At the federal level, the Administrative Rulemaking Reform Act (S-3297) aims to improve the production of regulations by federal agencies by increasing the opportunities for public participation, by congressional review of agency rules and by expanding judicial review.

It is to be hoped that these measures will help, but a paranoid surgeon must be very skeptical of their effectiveness. In the current War of the Regulation the federal establishment seems to be dedicated to bringing about total governmental control of health care in the United States and I greatly fear we are losing the war.

As has been emphasized in recent addresses by Director Rollins Hanlon and President Frank Stinchfield of the American College of Surgeons, surgery and surgeons are under attack by the federal establishment as part of the battle plan in this war. To paraphrase Rollins Hanlon, the insidious, mindless notion that surgical therapy, much of which is alleged to be unnecessary, is the major cause of rising health care costs must be exposed as the absurd fallacy that it is. Hanlon urges all surgeons to set the facts concerning proposed operations and other treatments lucidly and fully in front of patients so that they may participate intelligently with full information in the decision to proceed or not with a recommended course of treatment, especially elective surgical operation.

Frank Stinchfield has issued a clarion call to surgeons in all specialties to unite in the common cause of firmly opposing the attack on surgery currently being made by the federal establishment and the media.

Let all Fellows of the Southern Surgical Association respond to the leadership of our great College of Surgeons with vigorous support of the College and its programs! Let us carry factual information to our patients and address every available audience to countermand malicious propaganda! Let us form with the College a unified front against this War of the Regulation and this creeping socialism that would undermine freedom in our country and destroy the high quality of American surgery!

Cardiac Function at Rest and During Exercise in Normals and in Patients with Coronary Heart Disease:

Evaluation by Radionuclide Angiocardiography

STEPHEN K. RERYCH, M.D., PETER M. SCHOLZ, M.D., GLENN E. NEWMAN, M.D.,
DAVID C. SABISTON, JR., M.D., ROBERT H. JONES, M.D.*

From the Department of Surgery,
Duke University Medical Center,
Durham, North Carolina

This study demonstrates that radionuclide angiocardiography provides a simple and noninvasive approach for evaluation of myocardial function. Previous work concerning myocardial performance has been generally conducted with the patient in the supine position. Radionuclide angiocardiograms were performed in the present study at rest and during exercise in 30 normal subjects and in 30 patients with ischemic coronary artery disease. There were 30 normal controls (Group I), ten with single coronary artery disease (Group II), and 20 patients with multiple vessel coronary disease (Group III). All subjects were studied in the erect posture on a bicycle ergometer. In the *normal* controls, the mean heart rate doubled and the cardiac output tripled during exercise. Intensive training can lead to extraordinary levels of cardiac performance as shown in a world-class athlete who during peak exercise attained a heart rate of 210, an ejection fraction of 97%, and a cardiac output of 56 liters per minute. In the patients with coronary artery disease, both groups were able to increase cardiac output to approximately twice the resting value. The magnitude of increase in blood pressure during exercise was not significantly different in the three groups. However, definite changes were present in the end-diastolic volume at rest compared with exercise. The mean end-diastolic volume at rest was 116 and rose to 128 ml in Group I, 93 rising to 132 ml in Group II, and 138 increasing to 216 ml in Group III. The stroke volume increased comparably in all three groups, but the ejection fraction from rest to exercise showed a marked contrast in the controls compared to those with multivessel coronary disease. The ejection fraction rose in Group I from 66 to 80% during exercise, while in Group II it fell from 69 to 67%, and in Group III from 60 to 46%. These findings indicate that patients with ischemic myocardial disease respond to the stress of exercise by cardiac dilatation to maintain or increase stroke volume at increased heart rates. Moreover, the magnitude of this response appears to be greatest in patients with left main coronary artery stenosis. This approach for evaluating myocardial function during exercise provides useful data of importance in selecting medical versus surgical management of patients with ischemic coronary artery disease.

THE RECENT DEVELOPMENT of radionuclide angiocardiography provides a simple approach useful for evaluating patients during submaximal and maximal exercise.[4,16,24,31,34] The purpose of this study is to document the hemodynamic response in normal erect subjects and patients with myocardial ischemia due to coronary artery disease during maximal and submaximal exercise on the bicycle ergometer.

Radionuclides which distribute in the myocardium proportional to coronary blood flow have been used in exercising patients to evaluate regional perfusion disturbances.[22,25,35] Experimental observations have suggested that regional abnormalities of left ventricular function may reflect myocardial ischemia.[26] The present study was designed to evaluate cardiac performance by the first transit of a radionuclide bolus through the central circulation to measure the cardiac output, pulmonary transit time, pulmonary blood volume, left ventricular end-diastolic volume, and ejection fraction throughout the cardiac cycle. Exercise in the erect position was selected because of the similarity to daily activities which commonly impose exercise stress upon patients. The radionuclide procedure used in this study provides measurements during rest and exercise with accuracy and simplicity and is quite practical for routine clinical use.

Methods

Study Groups

Radionuclide angiocardiograms were obtained in 60 subjects who were admitted to Duke University

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

* Investigator, Howard Hughes Medical Institute.

Supported by NIH Grant No. 5 R01 HL 09315-14.

0003-4932-78-0500-0449-0125 © J. B. Lippincott Company

TABLE 1. *Hemodynamic Values in 30*

Subjects	Sex	Age (yrs)	BSA (m²)	Heart Rate (beats/min)		Mean Blood Pressure (mm/Hg)		C.O. (L/min)		C.I. (L/min/m²)		E.F.		EDV (ml)	
				Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1. D.P.	M	27	1.96	90	140	86	93	6.9	9.4	3.5	4.8	.62	.83	112	81
2. J.S.	M	27	2.15	65	168	76	113	6.3	20.9	2.9	9.7	.72	.82	135	152
3. N.P.	F	27	1.48	86	180	97	113	5.1	13.0	3.4	8.8	.68	.77	88	94
4. S.K.	F	29	1.36	80	170	67	118	4.7	11.8	3.5	8.6	.64	.83	92	83
5. J.M.	F	30	1.72	82	173	88	110	4.4	14.8	2.6	8.6	.64	.76	85	112
6. P.L.	M	34	2.07	100	180	94	101	7.9	21.5	3.8	10.4	.66	.83	119	144
7. J.A.	M	36	1.90	60	164	93	140	4.7	18.0	2.5	9.5	.79	.85	99	129
8. A.S.	M	43	1.94	65	160	113	119	5.6	16.9	3.4	8.7	.70	.80	117	132
9. L.J.	F	48	1.81	90	158	89	127	4.0	11.5	2.2	6.4	.66	.76	67	96
10. D.J.	M	48	1.74	85	175	107	100	5.5	15.3	3.1	8.8	.52	.69	123	126
11. G.K.	M	25	1.90	80	180	86	120	6.0	20.8	3.2	11.0	.67	.88	113	131
12. D.H.	F	53	1.76	115	156	130	137	5.8	10.2	3.3	5.8	.76	.84	66	78
13. H.R.	M	60	2.20	86	162	92	109	6.5	18.0	3.0	8.2	.63	.85	144	131
14. G.H.	F	31	1.76	120	150	93	103	6.4	14.1	3.6	8.0	.63	.80	100	118
15. P.S.	M	33	1.91	80	180	96	109	6.7	25.2	3.4	13.2	.56	.77	146	178
16. G.P.	F	29	1.72	72	188	98	109	3.6	13.5	2.1	7.9	.66	.69	76	104
17. J.F.	M	45	2.01	118	150	52	105	5.0	8.7	2.5	4.3	.65	.71	65	81
18. J.H.	M	24	2.00	65	210	82	110	6.9	27.8	3.4	13.9	.59	.88	180	150
19. B.B.	M	23	1.91	58	190	91	134	6.7	29.8	3.5	15.6	.71	.86	162	183
20. D.R.	M	25	1.96	68	195	100	100	6.3	24.9	3.2	12.7	.76	.83	121	154
21. A.S.	M	23	1.84	69	200	74	103	6.5	23.0	3.5	12.5	.69	.86	139	134
22. M.C.	M	23	1.90	70	190	117	127	7.6	28.7	4.0	15.1	.69	.86	158	175
23. C.R.	F	24	1.54	70	165	91	107	4.2	14.5	2.7	9.4	.67	.79	90	111
24. C.H.	M	24	1.90	73	150	92	122	6.1	23.0	3.2	12.1	.61	.84	137	183
25. J.C.	M	55	2.22	50	120	82	90	5.0	18.4	2.3	8.3	.63	.89	160	172
26. V.P.	M	29	1.92	95	210	99	123	7.0	19.8	3.7	10.3	.74	.73	100	129
27. B.B.	M	38	1.94	90	156	83	133	9.2	14.6	4.7	7.5	.73	.75	140	125
28. S.L.	M	25	1.78	70	160	82	105	4.2	10.9	2.4	6.1	.58	.72	103	95
29. C.P.	F	31	1.74	102	152	94	107	7.1	12.6	4.1	7.3	.60	.72	116	115
30. J.K.	F	36	1.45	90	156	81	95	7.7	13.7	5.3	9.4	.56	.64	153	137

	REST	EXERCISE	P
Heart Rate (beats/min)	81±18	170±21	$<10^{-9}$
Cardiac Output (L/min)	6.0±1.3	17.5±6.0	$<10^{-9}$
Pulmonary Transit Time (sec)	6.5±1.2	2.8±0.7	$<10^{-9}$
Pulmonary Blood Volume (ml)	640±151	776±264	<.01

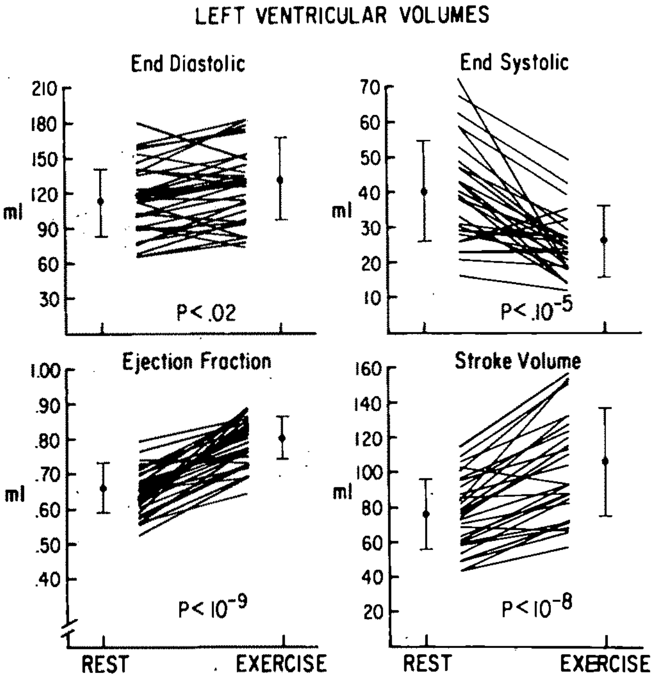


FIG. 1. Effects of exercise on left ventricular function in normal erect subjects. Mean age 34 years. (Ī represents mean values and standard deviation of the mean from rest to exercise).

Medical Center over a period from September 1976 to August 1977. There were 30 normal controls (Group I). In addition 30 patients were evaluated for chest pain, in whom a diagnosis of coronary artery disease was established. Ten of these patients had significant *single vessel* coronary artery disease (Group II), and 20 had *multi-vessel* coronary involvement (Group III).

The mean age of the controls in Group I was 34 years with a range of 23–60 years. Twenty subjects were male and ten were female with a mean body surface area of 1.85 m.[2] None of these controls had a history of chest pain, hypertension, myocardial infarction, or documented infarction on electrocardiogram. The history and physical examination in each were negative for other diseases related to the cardiopulmonary system.

Each patient within Groups II and III had a baseline evaluation consisting of electrocardiogram, chest film, and coronary arteriography, as well as hematologic and chemical blood profiles. In addition, Bruce stress treadmill testing was performed prior to cardiac catheterization.[5] Resting and exercise radionuclide studies were performed either one or two days prior

Normal Subjects at Rest and Exercise

EDV (ml/m²)		SV (ml)		SV (ml/m²)		ESV (ml)		ESV (ml/m²)		PTT (sec)		PBV (ml)		PBV (ml/m²)	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
57	41	69	67	35	34	43	14	22	7	5.4	3.0	621	470	317	240
63	71	97	124	45	58	38	27	18	13	7.5	2.7	789	940	367	437
59	64	60	72	41	49	28	22	19	15	4.4	2.4	374	520	253	351
68	61	59	69	43	51	33	14	24	10	4.9	2.1	386	411	284	302
49	65	54	85	31	49	31	27	18	16	5.5	2.4	403	590	235	343
57	70	79	120	38	58	40	24	19	12	6.2	3.1	816	860	394	415
56	68	78	110	41	58	21	19	11	10	7.8	2.4	607	719	320	378
60	68	88	105	45	54	29	27	15	14	7.0	2.1	655	591	338	304
37	53	44	73	24	40	23	23	13	13	6.9	2.8	456	537	252	297
71	72	64	87	37	50	59	39	34	22	7.7	4.2	700	1068	402	613
59	69	75	116	39	61	38	15	20	8	6.5	2.0	654	694	344	365
38	44	50	66	28	38	16	12	9	7	5.4	3.2	522	544	297	309
52	60	76	111	35	50	38	20	17	9	7.4	2.8	802	840	364	382
57	67	61	94	35	53	39	24	22	14	5.5	2.7	584	635	332	361
76	93	82	133	43	70	64	45	34	24	5.9	2.3	645	966	338	506
44	60	50	72	29	42	26	32	15	19	—	—	—	—	—	—
32	40	42	58	21	29	23	24	11	12	6.5	3.7	542	535	269	266
90	75	106	132	53	66	74	18	37	9	6.8	1.3	782	602	391	301
85	96	115	157	60	82	47	25	25	13	6.7	3.0	748	1490	392	780
62	79	92	128	47	65	29	26	15	13	6.5	2.5	679	1038	347	529
76	73	96	115	52	63	43	19	23	10	6.5	3.1	704	1188	383	646
83	92	109	151	57	79	49	25	26	13	7.1	2.1	902	1004	475	528
58	72	60	88	39	57	30	23	19	15	6.0	2.8	420	677	273	439
72	96	84	154	44	81	53	29	28	15	7.4	2.5	753	960	396	505
72	77	101	153	46	69	59	19	27	9	9.6	4.0	806	1225	363	552
52	67	74	94	39	49	26	35	14	18	5.3	1.8	622	594	324	309
72	64	102	94	53	48	38	31	20	16	4.8	2.6	736	633	379	326
58	53	60	68	34	38	43	27	24	15	6.0	3.0	420	537	236	307
67	66	70	83	40	48	47	32	27	18	5.6	4.6	665	967	382	556
106	94	86	88	59	61	67	49	46	34	6.8	2.9	875	662	603	456

to the catheterization-angiocardiographic study or one to two days prior to elective surgical saphenous vein bypass grafting in those who had arteriograms previously. Propranolol was discontinued 36–48 hours prior to radionuclide studies and nitroglycerin was not administered for a period of eight hours prior to testing. No patient with coronary artery disease had a recent myocardial infarction, but 13 patients had prior myocardial infarction documented by a 12-lead resting electrocardiogram, vectorcardiogram, or positive muscle band CPK isoenzymes. Cardiac catheterization consisted of standard left ventriculography for determination of wall motion abnormalities, ejection fraction, volume and pressure data in addition to coronary arteriography. Each of the ten patients in Group II with "significant" one vessel coronary artery disease had a 75% or greater stenosis of a major coronary artery demonstrated by arteriography. The mean age in this group was 47 years (range 34–69). Five patients were male and five were female with a mean body surface area of 1.76 m². The 20 patients in Group III had significant lesions of more than one major coronary artery, including five patients with significant left main stenosis (>75%). The mean age of this group was 53 years (range 38–67). Nineteen patients in Group III were male and one female with an average group body surface area of 1.93 m². In the two groups with documented coronary artery disease, none had evidence of valvar heart disease. In those patients with documented myocardial infarction, exercise radionuclide testing was performed at least three to four months after infarction.

Studies were performed in the erect sitting position during rest and exercise on a Tunturi bicycle ergometer.® After informed consent was obtained from each subject, baseline supine measurements of blood pressure using a standard sphygmomanometer and heart rate as recorded from the modified limb lead CM-5 were recorded. Local anesthesia was used over the skin area of either the external jugular or antecubital vein by injection of 0.5 ml of 1% Xylocaine, and a 20 gauge Teflon® catheter was inserted into the corresponding vein. This was connected with a three-way stopcock, 20 inch venotube, and a 20 ml syringe filled with normal saline. The patients were then placed on the bicycle ergometer in the erect position and imaged in the anterior projection with a Baird Atomic System Seventy-Seven multicrystal gamma camera.® Exercise studies preceded rest studies in all patients and subjects. Prior to exercise, the baseline heart rate and blood pressure were recorded. The electrocardiogram was monitored via telemetry throughout the exercise and recovery periods. Blood pressures were recorded by sphygmomanometer at one minute intervals during

TABLE 2. *Hemodynamic Response to Exercise in*

				Heart Rate (beats/min)		Mean Blood Pressure (mm/Hg)		C.O. (L/min)		C.I. (L/min/m²)		Ejection Fraction		EDV (ml)		EDV (ml/m²)		SV (ml)	
Patients	Sex	Age Years	BSA (m²)	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1	F	39	1.64	78	112	90	107	4.7	9.1	2.8	5.5	.66	.69	91	117	55	71	60	81
2	F	51	1.76	94	140	98	117	5.3	15.3	3.0	8.7	.80	.68	70	161	40	91	56	109
3	F	49	1.46	100	130	96	126	6.7	9.7	4.6	6.6	.70	.71	95	105	65	72	67	75
4	F	37	1.71	100	188	79	132	6.0	8.3	3.5	4.9	.86	.72	70	83	37	49	60	60
5	M	44	1.83	78	138	78	131	3.9	9.8	2.1	5.4	.58	.58	86	123	47	67	50	71
6	M	48	1.95	95	150	85	122	7.6	18.6	3.9	9.5	.80	.79	94	167	48	86	80	124
7	M	34	1.84	118	172	78	115	6.6	18.7	3.6	10.2	.54	.71	104	154	57	84	56	109
8	F	61	1.54	90	140	119	133	4.6	7.3	3.0	4.7	.70	.60	73	86	47	56	51	52
9	M	38	1.95	63	100	99	106	4.4	10.3	2.3	5.3	.57	.61	123	168	63	86	70	103
10	M	69	1.94	58	88	99	107	4.8	8.9	2.5	4.6	.66	.66	125	155	64	80	83	102

DMI diaphragmatic myocardial infarction, AMI anterior wall myocardial infarction, N no previous infarction, * positive stress treadmill test, (−)A negative adequate, (−)I negative inadequate, NYHA New York Heart Association functional classification, O normal wall motion, + abnormal wall motion (dyskinesia), NC no change.

exercise and every two minutes during the recovery period. Normal subjects were exercised to 85% of the maximal predicted heart rate for their age. In patients with known coronary artery disease as determined by cardiac catheterization or suspected coronary artery disease on the basis of a positive stress treadmill test, end points in exercise were defined as the onset of typical angina associated with a ≥1 mv depression of the S-T segment as recorded by electrocardiogram, life-threatening dysrhythmias, hypotension, muscle fatigue, or attainment of target heart rate. When any one of these events occurred, a bolus of 15 mCi technetium-99m pertechnetate was immediately injected, and counts were recorded at 50 msec intervals for one minute. Patients and subjects were then allowed to recover in the supine position until the EKG, heart rate, and blood pressure returned to baseline values. Prior to the injection of the second bolus of 15 mCi technetium-99m pertechnetate, a one minute background count over the precordium was obtained with the subject erect. The resting study was then performed at counting intervals of 50 msec.

	Rest	Exercise	P
Heart Rate (beats/min)	87±18	131±25	$< 10^{-6}$
Cardiac Output (L/min)	5.4±1.2	11.6±4.2	< .001
Pulmonary Transit Time (sec)	6.6±1.5	3.7±0.8	$< 10^{-5}$
Pulmonary Blood Volume (ml)	589±170	718±286	< .05

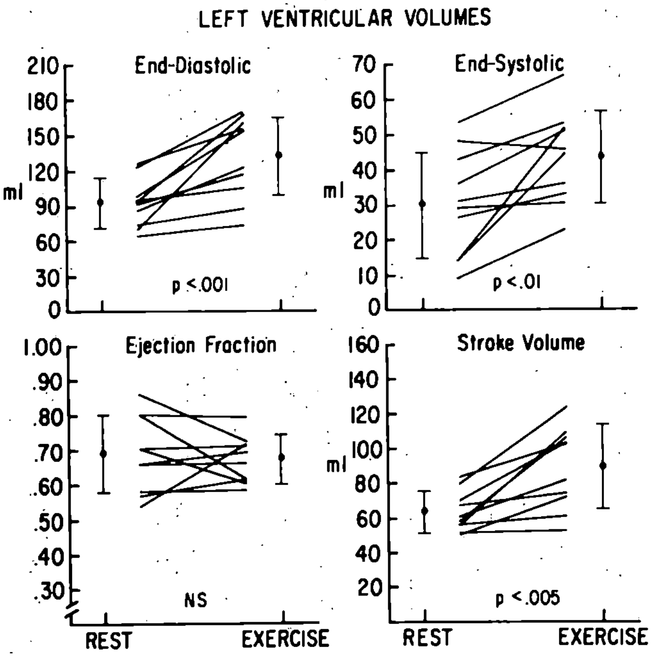


FIG. 2. Response to exercise in 10 patients with single vessel coronary artery disease (Mean age 47 years). During exercise mean ejection fraction decreases slightly while end-systolic volume, end-diastolic volume, and stroke volume all increase; NS = not significant.

Instrumentation and Data Processing

The Baird Atomic System Seventy-Seven computerized multicrystal gamma camera® was used for all dynamic studies. This instrument permitted counting rates greater than 400,000 counts per second, and counting intervals as brief as 50 msec. After initial computer correction of the data, the next step in data processing was to relate observed counts to discrete cardiac regions. A method has been developed to define borders of cardiac chambers, which depends upon a description of the time function of counts observed in many small regions over the precordium.[17] Individual cardiac chamber delay with bolus transit of tracer reflected by the time description permits accurate delineation of cardiac chamber boundaries. A degree of anatomic overlap occurs in some of the adja-

Patients with One Vessel Coronary Artery Disease

SV (ml/m^2)		ESV (ml)		ESV (ml/m^2)		PTT (sec)		PBV (ml)		PBV (ml/m^2)					Radionuclide Wall Motion	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Myocard. Infarction	Bruce Treadmill Stress Test	NYHA Class.	Rest	Exercise
37	49	31	36	19	22	5.8	2.5	450	377	275	230	N	*	IV	0	NC
32	62	14	52	8	30	7.6	4.1	671	1046	381	594	N	*	IV	0	+
46	51	29	30	20	21	5.3	3.0	589	483	404	331	N	−(A)	IV	0	NC
35	35	10	23	6	13	5.9	4.0	590	552	345	323	N	−(I)	IV	0	+
27	39	36	51	20	28	6.6	3.8	430	621	235	339	N	*	IV	0	NC
41	54	14	44	7	23	5.8	3.2	735	991	360	508	N	−(I)	IV	0	+
30	59	48	45	26	24	7.9	3.8	871	1187	473	645	AMI	−(A)	I	+	NC
33	34	26	33	17	21	4.1	3.1	314	377	204	245	N	*	III	0	+
36	53	53	66	27	34	7.3	4.4	539	754	276	387	DMI	−(I)	IV	0	NC
43	53	43	53	22	27	9.4	5.3	751	794	387	409	N	*	IV	0	NC

cent cardiac chambers in any projection, and complex curves with several individual components are recorded over these adjacent cardiac regions. A computer technique has been developed using the first derivative of data to separate complex curves into individual components and to characterize each individual curve by the total counts and by mean transit time. The accurate delineation of anatomic regions which results is particularly important for the calculation of the ejection fraction.

Time activity curves from individual cardiac chambers may be used to calculate cardiac output, mean chamber volumes, and mean chamber transit time. A comparison of the systolic and diastolic counts within the left ventricle permits calculation of the ejection fraction. Observations in 33 patients demonstrated a correlation coefficient of 0.89 between this radionuclide technique and standard contrast biplane ventriculography. Ventricular volume changes during a single cardiac contraction were obtained by adding data from several cardiac contractions recorded at the time when tracer was maximal within the chamber. Phasic relationships to the cardiac cycle are retained, and the resulting curve which reflects count changes during the average cardiac cycle is related to changes in chamber volume by subtraction of background counts. Background counts are obtained by summing data from the initial transit of tracer just before and just after the time of maximal activity within the specific chamber. In addition to the quantitative data described, images are obtained of the initial tracer transit to permit appreciation of blood flow patterns. Supraimposition of 50 msec images from several cardiac cycles which retain phasic relationships throughout systole and diastole provide high count rate images reflecting chamber motion during a typical cycle. The images, which can be visualized in a dynamic cine format or static mode, permit assessment of wall motion abnormalities. Images are complementary with the quantitative data, and the greatest hemodynamic information results from a combined expression of the data in these two forms.

Validity of Volumetric Analysis

A new technique has been developed in this laboratory for obtaining cardiac output from the initial passage of tracer through the left ventricle in the anterior projection. This method employs standard angiographic planimetry of the static left ventricular end-diastolic volume image. End-diastolic volume is obtained by using the length-area measurement implied by the prolated ellipsoid model of revolution described by Dodge and associates.[7] A regression equation from 33 patients studied prior to catheterization gave the appropriate corrected end-diastolic volume. The correlation coefficient was 0.89. Stroke volume equals the product of end-diastolic volume and ejection fraction. The difference between stroke volume and end-diastolic volume provides the end-systolic volume. This volumetric technique using the first transit of radionuclide bolus was further verified in 33 normal subjects at rest and immediately following exercise with simultaneous determination of cardiac output using indocyanine green dye. Stroke volume determined from the computer generated ejection fraction and planimetered end-diastolic volume image revealed a correlation coefficient of 0.87. The corresponding cardiac outputs determined by both methods showed a correlation coefficient of 0.95.

The following list summarizes mathematical techniques for determination of left ventricular function

TABLE 3. *Hemodynamic Values in Patients with*

Patients	Sex	Age Years	Body Surface Area BSA (m²)	Heart Rate (beats/min) Rest	Heart Rate (beats/min) Exercise	Mean Blood Pressure (mm/Hg) Rest	Mean Blood Pressure (mm/Hg) Exercise	Cardiac Output C.O. (L/min) Rest	Cardiac Output C.O. (L/min) Exercise	Cardiac Index C.I. (L/min/m²) Rest	Cardiac Index C.I. (L/min/m²) Exercise	Ejection Fraction Rest	Ejection Fraction Exercise	End Diastolic Volume EDV (ml) Rest	End Diastolic Volume EDV (ml) Exercise	End Diastolic Volume Index EDV (ml/m²) Rest	End Diastolic Volume Index EDV (ml/m²) Exercise	Stroke Volume SV (ml) Rest	Stroke Volume SV (ml) Exercise
1	M	67	1.91	70	120	76	106	4.6	10.3	2.4	5.4	.57	.27	116	317	61	166	66	86
2	M	48	1.85	68	82	79	97	5.2	7.8	2.8	4.2	.77	.75	100	127	54	69	77	96
3	M	58	1.96	77	120	81	67	7.5	6.2	3.8	3.2	.53	.31	185	167	94	85	98	52
4	M	42	1.88	105	156	89	127	6.4	10.1	3.4	5.4	.35	.33	173	196	92	104	61	65
5	M	59	1.81	65	110	103	115	4.6	15.3	2.5	8.5	.69	.52	103	267	57	146	71	139
6	M	46	1.91	96	120	106	116	6.5	9.2	3.4	4.8	.34	.31	200	247	105	129	68	77
7	M	64	1.88	68	108	77	104	4.5	9.2	2.4	4.9	.76	.48	87	178	46	95	66	85
8	F	60	1.51	80	120	94	150	5.9	8.6	3.9	5.7	.76	.55	97	131	64	87	74	72
9	M	59	1.80	60	88	83	113	3.8	9.5	2.1	5.3	.69	.56	93	187	52	104	64	108
10	M	50	1.97	70	100	113	147	5.6	15.6	2.8	7.9	.60	.52	123	264	62	134	80	156
11	M	38	2.21	70	130	84	121	7.1	9.9	3.2	4.5	.43	.28	238	271	108	123	102	76
12	M	60	1.85	60	144	99	122	7.0	17.4	3.8	9.4	.68	.52	171	232	92	125	115	121
13	M	42	2.21	90	156	92	156	5.2	19.7	2.4	8.6	.58	.46	100	274	45	124	58	126
14	M	56	1.85	95	112	98	130	5.6	10.4	3.1	5.6	.70	.43	85	216	46	117	59	93
15	M	41	1.95	55	78	93	113	4.1	6.8	2.1	3.5	.71	.64	106	147	54	75	75	94
16	M	40	2.32	86	152	87	127	9.6	17.0	4.1	7.4	.36	.32	309	349	133	150	111	112
17	M	49	1.96	95	150	95	112	7.1	13.7	3.6	6.9	.76	.69	93	132	47	67	71	91
18	M	57	1.93	54	150	108	127	4.9	16.8	2.5	8.7	.46	.39	196	287	102	149	90	112
19	M	60	1.91	70	84	119	134	3.7	3.9	2.0	2.0	.59	.30	91	143	48	81	53	46
20	M	59	1.91	70	90	93	101	4.5	9.4	2.4	4.9	.70	.62	92	168	48	88	64	104

DMI Diaphragmatic myocardial infarction, AMI Anterior myocardial infarction, N No previous infarction, (L.M.) Left main coronary stenosis, * Positive stress treadmill test, (−)I Negative inadequate, NYHA New York Heart Association functional classification, O Normal wall motion, + Abnormal wall motion (dyskinesia), ++ New area of abnormal wall motion (dyskinesia).

from data obtained by the first passage of tracer through the central circulation.

1. ejection fraction (EF) percent

$$= \frac{\text{EDV counts} - \text{ESV counts}}{\text{EDV counts}} \times 100\%$$

2. left ventricular end-diastolic volume (LVEDV)

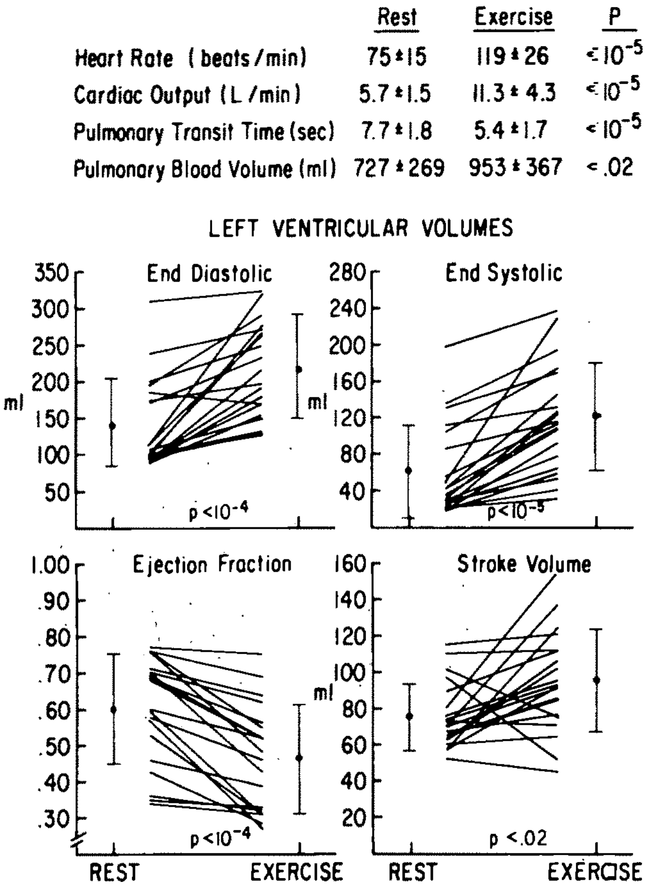
$$= \frac{0.85\ A^2}{l}$$

The radionuclide end-diastolic image was used to obtain the area (A) by planimetry and the length (l) by direct measurement.

3. stroke volume = LVEDV × EF
4. end-systolic volume = LVEDV − SV
5. cardiac output = SV × HR

Mean blood pressures recorded simultaneously with the rest and exercise study were used to calculate the mean systemic arterial pressure by the sum of one third the pulse pressure and end-diastolic pressure.[10]

The pulmonary mean transit time in seconds was obtained by the difference in the mean transit times



	Rest	Exercise	P
Heart Rate (beats/min)	75±15	119±26	$<10^{-5}$
Cardiac Output (L/min)	5.7±1.5	11.3±4.3	$<10^{-5}$
Pulmonary Transit Time (sec)	7.7±1.8	5.4±1.7	$<10^{-5}$
Pulmonary Blood Volume (ml)	727±269	953±367	<.02

←

FIG. 3. Effects of exercise in 20 patients with more than one vessel coronary artery disease (Mean age 53 years). Note that during exercise there are significant increases seen in end-diastolic volume and end-systolic volume while ejection fraction is depressed.

More Than One Vessel Coronary Artery Disease

Stroke Volume Index SV (ml/m²)		End Systolic Volume ESV (ml)		End Systolic Volume Index ESV (ml/m²)		Pulmonary Transit Time PTT (sec)		Pulmonary Blood Volume PBV (ml)		Pulmonary Blood Volume Index PBV (ml/m²)		Bruce Treadmill Stress Test			Radionuclide Wall Motion	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Myocard. Infarction	Treadmill Stress Test	NYHA Class	Rest	Exercise
35	45	50	231	26	121	9.6	6.7	766	948	401	496	N(L.M.)	*	III	0	+
42	52	23	32	12	17	6.7	3.3	581	431	314	233	DMI	*	IV	0	+
50	27	87	115	44	59	8.4	3.7	1055	383	538	196	DMI(L.M.)	*	III	+	++
32	35	112	131	60	70	5.6	4.9	598	825	318	439	AMI	*	IV	+	++
39	77	32	128	18	71	6.5	6.8	498	1734	275	958	DMI(L.M.)	*	II	0	+
36	40	132	171	69	90	8.0	5.1	869	781	455	409	DMI	*	III	+	++
35	45	21	93	11	49	9.1	6.8	683	1042	363	554	N	*	IV	0	+
49	48	23	59	15	39	6.2	5.1	610	731	404	484	N	*	IV	0	+
36	60	29	79	16	44	8.6	7.5	549	1188	305	660	N	*	IV	0	+
41	79	43	108	22	55	5.9	4.0	551	1040	271	512	DMI	*	III	+	++
46	34	136	195	62	88	13.5	8.5	1598	1403	723	635	AMI,DMI(L.M.)	−(I)	III	+	++
63	65	55	111	30	60	7.2	4.0	836	1162	452	628	N	*	II	0	+
26	57	42	148	19	67	7.3	2.6	630	850	280	373	N	*	II	0	+
32	63	25	123	14	66	7.2	4.9	678	848	366	458	N	*	III	0	+
38	48	31	53	16	27	7.1	5.2	485	586	249	300	DMI	*	III	0	+
48	48	198	237	85	102	7.1	5.9	1133	1672	488	721	DMI	−(I)	I	+	++
36	46	22	41	11	21	5.0	3.6	588	819	302	418	AMI	*	IV	0	+
47	58	106	175	55	91	8.1	4.4	658	1233	341	634	DMI	*	II	+	++
28	24	38	108	20	57	9.3	8.7	579	564	303	295	N(L.M.)	*	IV	0	+
34	54	28	64	15	34	7.8	5.2	585	812	306	495	N	*	III	0	+

of the left atrial and pulmonary artery radionuclide curves. The mean transit time is directly related to volume and inversely proportional to flow. Therefore, the pulmonary blood volume (in ml) is calculated by multiplying the cardiac output (in ml/sec) by the pulmonary mean transit time (in sec). The mean pulmonary transit time in normal subjects was 6.5 seconds. The corresponding pulmonary blood volume was 650 ml, which is approximately 11% of the cardiac output.

Measurements and Statistical Analyses

The paired student t-test was used to compare differences in individual rest and exercise measurements in each group. Significance of difference between groups was obtained by the comparison of means (unpaired t-test). Significance of data was determined at the level of $p < 0.05$.

Results

For purposes of analysis, the 60 subjects were divided into three groups. There were 30 normal controls (Group I), ten patients with documented one vessel coronary artery disease (Group II), and 20 patients with documented coronary artery disease involving more than one vessel (Group III). Within Group II, two patients were known to have sustained myocardial infarction prior to study. In Group III, 11 patients had sustained infarction prior to study.

The hemodynamic data for control subjects at rest and exercise are depicted in Table I and Figure 1. The electrocardiogram was normal at rest and no abnormalities were noted during exercise. Increased wall motion was noted in all normal subjects from rest to exercise. Although biological variation occurred among individual members within the group, a statistically significant change occurred in all left ventricular function measurements. For example, mean heart rate increased by 110% from rest to exercise ($p < 10^{-9}$). The corresponding increase in cardiac output was 192% ($p < 10^{-9}$). The mean increase in ejection fraction was 0.66 at rest to 0.80 at exercise ($p < 10^{-9}$). Stroke volume also showed a significant increase from 76 ± 20 ml to 102 ± 30 ml ($p < 10^{-8}$). On the other hand, the increase in end-diastolic volume was modest, with the mean value at rest being 116 ± 31 ml rising to 128 ± 31 ml at exercise ($p < 0.02$). End-systolic volume decreased from 40 ± 15 ml to 26 ± 9 ml ($p < 10^{-5}$). Pulmonary transit time also decreased significantly ($p < 10^{-9}$). However, pulmonary blood volume showed a mean increase from 640 ± 151 ml to 776 ± 264 ml ($p < 0.01$). Mean blood pressure increased in all normal subjects ($p < 10^{-6}$).

The hemodynamic data for each patient studied in

TABLE 4. *Mean Hemodynamic Changes In Three Study Groups*

	Mean		Standard Deviation		Standard Error		Paired *t*-Statistics	Mean % Change from Rest to Exercise
	Rest	Exercise	Rest	Exercise	Rest	Exercise		
Normal Subjects, Mean Age—34 years, Mean Body Surface Area—1.85 m^2								
Heart Rate (beats/min)	81	170	±13	±21	3.21	3.75	$<10^{-9}$	↑110
Mean Blood Pressure (mm/Hg)	91	113	±15	±13	2.69	2.40	$<10^{-6}$	↑ 24
C.O. L/min	6.0	17.5	±1.3	±6.0	0.24	1.09	$<10^{-9}$	↑192
C.I. L/min/m^2	3.3	9.4	±0.7	±2.9	0.13	0.52	$<10^{-9}$	↑185
Ejection Fraction	0.66	0.80	±0.06	±0.07	0.01	0.01	$<10^{-9}$	↑ 21
EDV (ml)	116	128	±31	±31	5.60	5.72	<0.02	↑ 10
EDV (ml/m^2)	63	69	±16	±15	2.94	2.73	<0.03	↑ 10
SV (ml)	76	102	±20	±30	3.68	5.40	$<10^{-8}$	↑ 34
SV (ml/m^2)	41	55	±10	±13	1.78	2.43	$<10^{-8}$	↑ 34
ESV (ml)	40	26	±15	±9	2.65	1.57	$<10^{-5}$	↓ 35
ESV (ml/m^2)	22	14	±8	±6	1.52	1.02	$<10^{-5}$	↓ 36
PTT (sec)	6.5	2.8	+1.2	±0.7	0.21	0.13	$<10^{-6}$	↓ 57
PBV (ml)	644	776	±152	±264	28.19	49.07	<0.01	↑ 20
PBV (ml/m^2)	345	416	±76	±130	14.05	24.14	<0.01	↑ 21
Patients with One Vessel Coronary Artery Disease, Mean Age—47 years, Mean Body Surface Area—1.76 m^2								
Heart Rate (beats/min)	87	131	±13	±25	5.80	7.80	$<10^{-6}$	↑ 51
Mean Blood Pressure (mm/Hg)	92	120	±13	±11	4.07	3.40	<0.0007	↑ 30
C.O. L/min	5.4	11.6	±1.2	±4.3	0.38	1.4	<0.001	↑115
C.I. L/min/m^2	3.1	6.5	±0.8	±2.1	0.24	0.67	<0.001	↑110
Ejection Fraction	0.69	0.67	±0.11	±0.07	0.03	0.02	NS	↓ 3
EDV (ml)	93	132	±20	±33	6.29	10.50	<0.001	↑ 42
EDV (ml/m^2)	52	74	±10	±15	3.17	4.38	<0.01	↑ 42
SV (ml)	63	89	±12	±24	3.71	7.61	<0.005	↑ 39
SV (ml/m^2)	36	50	±6	±11	1.88	3.40	<0.005	↑ 39
ESV (ml)	30	43	±15	±13	4.75	4.80	<0.01	↑ 43
ESV (ml/m^2)	17	24	±8	±6	2.43	1.84	<0.02	↑ 41
PTT (sec)	6.6	3.8	±1.5	±0.8	0.48	0.26	$<10^{-5}$	↓ 42
PBV (ml)	594	718	±169	±286	53.36	90.30	<0.05	↑ 21
PBV (ml/m^2)	334	401	±84	±140	26.58	44.33	NS	↑ 20
Patients with More than One Vessel Coronary Artery Disease, Mean Age—53 years, Mean Body Surface Area—1.93 m^2								
Heart Rate (beats/min)	75	119	±15	±26	3.30	5.89	$<10^{-5}$	↑ 59
Mean Blood Pressure (mm/Hg)	93	118	±12	±19	2.69	4.18	$<10^{-5}$	↑ 27
C.O. L/min	5.7	11.3	±1.5	±4.3	0.33	0.96	$<10^{-5}$	↑ 98
C.I. L/min/m^2	2.9	5.8	±0.7	±2.0	0.15	0.45	$<10^{-5}$	↑100
Ejection Fraction	0.60	0.46	±0.15	±0.15	0.03	0.03	$<10^{-4}$	↓ 23
EDV (ml)	138	216	±62	±66	13.79	14.84	$<10^{-4}$	↑ 57
EDV (ml/m^2)	71	111	±27	±30	6.00	6.62	$<10^{-4}$	↑ 56
SV (ml)	76	96	±18	±28	4.03	6.22	<0.02	↑ 21
SV (ml/m^2)	40	50	±9	±15	1.97	3.27	<0.01	↑ 25
ESV (ml)	62	120	±50	±59	11.15	13.22	$<10^{-5}$	↑ 94
ESV (ml/m^2)	31	61	±23	±28	5.09	6.15	$<10^{-5}$	↑ 97
PTT (sec)	7.7	5.4	±1.8	±1.7	0.41	0.38	$<10^{-5}$	↑ 30
PBV (ml)	727	953	±269	±367	60.04	82.08	<0.02	↑ 31
PBV (ml/m^2)	373	491	±114	±182	25.57	40.61	<0.02	↑ 32

Significance <0.05, NS Not statistically significant, ↑ Increase, ↓ Decrease.

Group II are shown in Table 2 and Figure 2. Eight of the ten patients were functional NYHA Class IV. Prior Bruce protocol stress treadmill tests were interpreted to show ischemic heart disease in five of the ten patients. In the remaining five patients, three had negative inadequate stress tests and two had negative adequate tests.

Radionuclide images of left ventricular contraction permitted assessment of wall motion at rest and exercise. The single patient (No. 7) in Group II, who had a wall motion abnormality at rest, had sustained a prior myocardial infarction and the abnormality did not change during exercise. Four patients with normal wall motion at rest developed segmental hypokinesia during exercise. In the remaining five patients with normal wall motion at rest, no discrete wall motion abnormality appeared during exercise. However, these patients failed to show the normal increase in wall motion during exercise, and the mean ejection fraction of .69 at rest showed an insignificant change to a mean of .67 during exercise. The mean end-diastolic volume increased from 93 ± 20 ml to 132 ± 33 ml ($p < 0.01$) during exercise. Whereas the mean end-systolic volume in normal subjects decreased with exercise, the

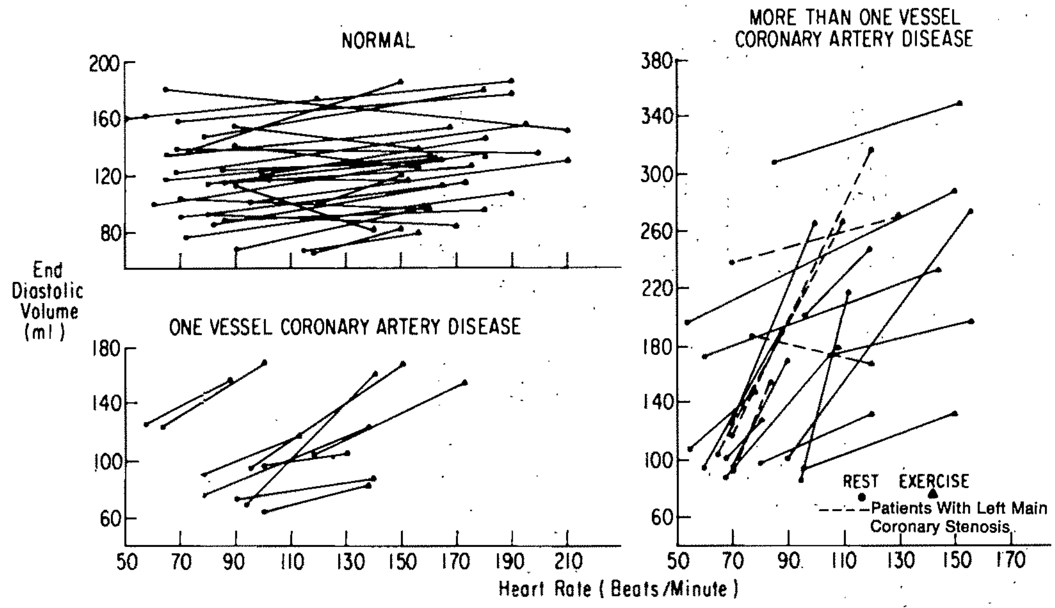


FIG. 4. Effects of increased heart rate upon left ventricular end-diastolic volume. The normal response reveals a slight variation; however, in patients with coronary artery disease and particularly patients with left main stenosis (except Patient 3, Group III), an increase in end-diastolic volume is observed.

mean end-systolic volume in patients in Group II increased from 30 ± 15 ml at rest to 43 ± 13 ml during exercise ($p < 0.01$).

The hemodynamic data for each patient in Group III are shown in Table 3 and Figure 3. Eleven of the 20 patients suffered prior myocardial infarction, and 18 had positive treadmill tests. Five patients had significant left main coronary artery stenosis. Seven patients exhibited abnormal wall motion at rest. However, all patients within the group exhibited a new area of segmental or global wall motion abnormality during exercise. All hemodynamic parameters changed significantly with exercise in this group. However, the most important changes occurred in end-diastolic volume, ejection fraction, and end-systolic volume. End-diastolic volume increased significantly ($p < 10^{-4}$) from 138 ± 62 ml at rest to 216 ± 66 ml at exercise. A corresponding increase was shown in end-systolic volume

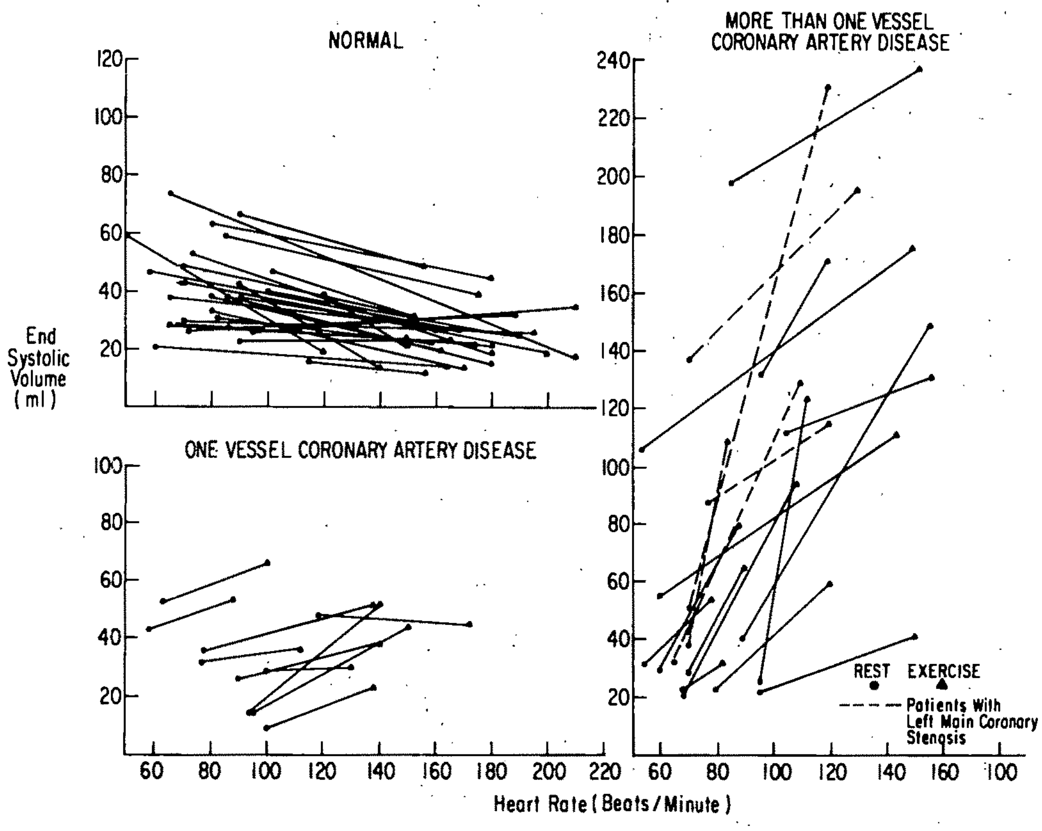


FIG. 5. Relationship between end-systolic volume and increases in heart rate. There is a decrease in end-systolic volume in the normal (except subject 7); however, in patients with one vessel (except Patient 7, Group II) and more than one vessel coronary artery disease, particularly left main stenosis, an increase in end-systolic volume is observed.

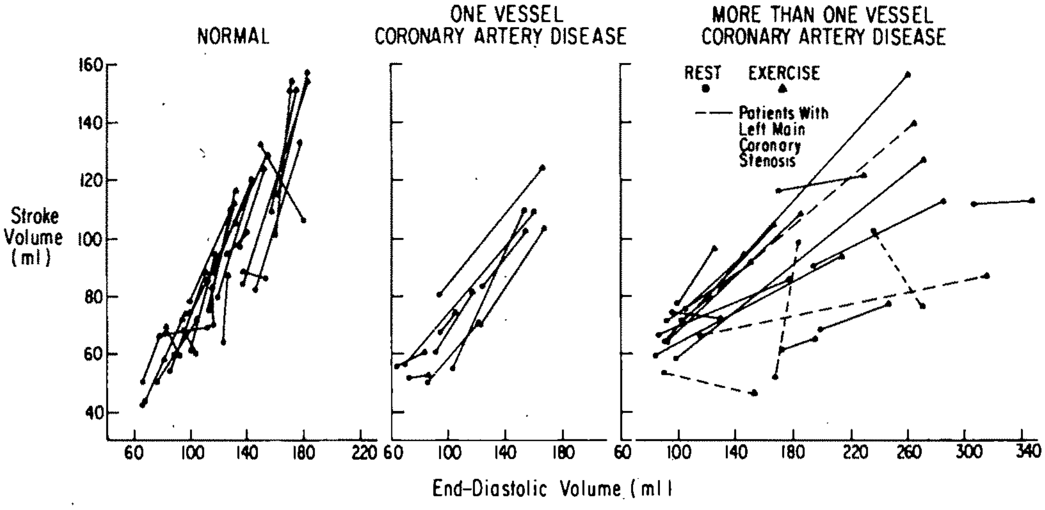


FIG. 6. Comparison of left ventricular function by plotting end-diastolic volume (initial diastolic fiber length) against stroke volume. The normal response demonstrates comparatively small increases in end-diastolic volume and results in a much greater increase in stroke volume. However, variation is observed in subjects 1, 4, 13, 18, 21, 27–30 in Group I. In patients with one vessel and more than one vessel coronary artery disease, a larger end-diastolic volume is needed to maintain stroke volume. In patients 8, 11, and 19 (Group III), an increase in end-diastolic volume results in a decrease in stroke volume. This suggests a descending limb to the Frank-Starling ventricular function curve.

from 62 ± 50 ml to 120 ± 50 ml ($p < 10^{-5}$). Moreover, the ejection fraction revealed a dramatic mean decrease of 0.60 at rest to 0.46 at exercise ($p < 10^{-4}$). A comparative summary of all measured hemodynamic parameters is presented in Table 4.

Changes in end-diastolic volumes with exercise occurred at different heart rates in Groups I–III (Fig. 4). Although the normal controls (Group I) show a statistically significant increase ($p < 0.02$) in end-diastolic volume, this occurred at a very high heart rate. However, in Groups II and III, a much greater increase in end-diastolic volume is observed ($p < .001$ in Group II and $p < 10^{-5}$ in Group III) at lower heart rates. Patients with left main stenosis demonstrate the most marked increments in end-diastolic volume with only a small change in heart rate from rest to exercise. The only exception to this observtion was Patient 3 in Group III, in whom end-diastolic volume fell with

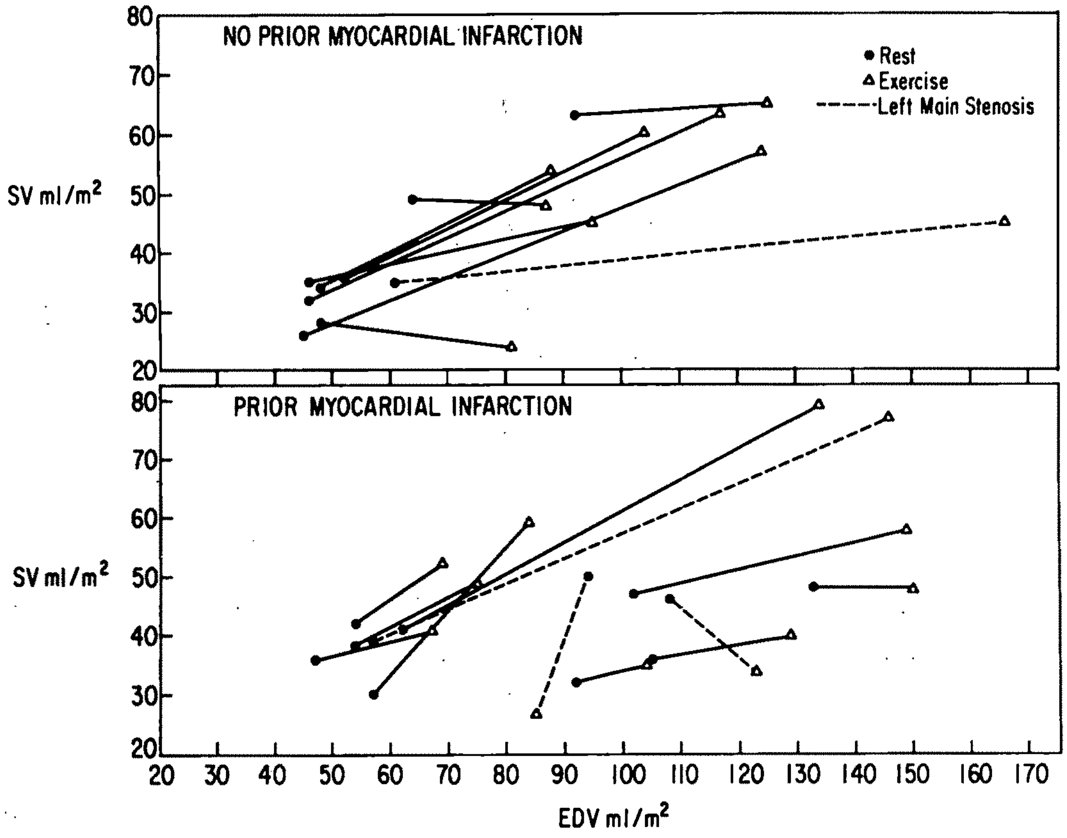


FIG. 7. End-diastolic volume index is compared to the stroke volume index in patients with more than one vessel coronary artery disease with and without prior myocardial infarction. All patients within this group demonstrated new areas of wall motion abnormalities at exercise not apparent at rest. Therefore, an ischemic response to exercise may be evoked even in patients with prior myocardial infarction.

exercise. However, this patient also became hypotensive during the exercise (Table 3).

The magnitude of change in end-systolic volume with exercise also occurred at different heart rates in the three groups (Fig. 5). The controls (Group I) show a significant decrease ($p < 10^{-5}$), whereas Groups II and III reveal statistically significant increases ($p < .01$ and $p < 10^{-5}$) at lower heart rates.

Ventricular function curves compare the end-diastolic volume required to achieve the stroke volume at rest and exercise in the three groups (Fig. 6). Large increases in end-diastolic volume from rest to exercise are required to maintain the stroke volume in Group III, and patients in Group II showed less increase in stroke volume at any end-diastolic volume in comparison to Group I. Patients 8, 11, and 19 in Group III actually decreased stroke volume with an increase in end-diastolic volume, and two of these patients had left main coronary artery stenosis.

Left ventricular function curves for patients in Group III with and without prior myocardial infarction are shown in Figure 7. With the exception of Patients 11 and 16, all had evidence of myocardial ischemia on the basis of a positive stress treadmill test. Furthermore, all patients revealed new areas of segmental or global wall motion abnormality during exercise which were not present at rest during radionuclide studies. These data suggest that myocardial ischemia can be demonstrated even in patients with myocardial fibrosis resulting from a previous myocardial infarction.

Data processed images of end systole superimposed on the image of the cardiac border during diastole document wall motion in a normal subject (A), a patient with one vessel coronary disease (B), and a patient with more than one vessel involvement (C) (Fig. 8). Wall motion was normal in the control subject at rest and during exercise. In patients B and C, wall motion was normal at rest, but obvious abnormalities appeared during exercise. The left ventricular volume curves show essentially normal resting ejection fractions and end-diastolic volumes in all three patients (Fig. 9). However, during exercise, the normal subject increased left ventricular ejection fraction with no change in end-diastolic volume and a decrease in end-systolic volume. In the patient with one vessel disease, decreased ejection fraction during exercise was associated with a moderate increase in both end-diastolic and end-systolic volume. In the patient with stenosis of more than one coronary artery, a large decrease in the ejection fraction was accompanied by a very large increase in end-diastolic and end-systolic volumes.

A statistical analysis of left ventricular function in the three groups is shown in Table 5. Comparison between the normal ventricles (Group I) and the patients with one vessel coronary disease (Group II) reveals a statistically significant lower heart rate ($p < 0.00002$), cardiac index ($p < 0.01$), and ejection fraction ($p < 0.00002$) in Group II during exercise. Moreover, the end-systolic volume index is larger at exercise in Group II ($p < 0.00002$). Left ventricular function at rest shows no significant differences between the two groups. Comparison between normal subjects (Group I) and patients with more than one vessel disease (Group III) at exercise reveals significantly lower heart rate, cardiac index, and ejection fraction in Group III. In addition, the end-diastolic volume index ($p < 10^{-8}$) and the end-systolic volume index ($p < 10^{-9}$) both were larger in Group III during exercise. At rest, the only significant difference between the groups was a larger end-diastolic volume index in Group III ($p < 0.05$). A comparison between patients with one vessel coronary disease and patients with more than one vessel stenosis reveals no difference in heart rate or cardiac index at rest and exercise. However, during exercise Group III has a lower ejection fraction ($p < 0.0002$) and a larger end-diastolic volume index ($p < 0.001$) and end-systolic volume index ($p < 0.0003$) than Group II. The only difference during rest was a larger end-diastolic volume index ($p < 0.05$) in Group III. The similar mean blood pressure in all groups suggests that left ventricular volume

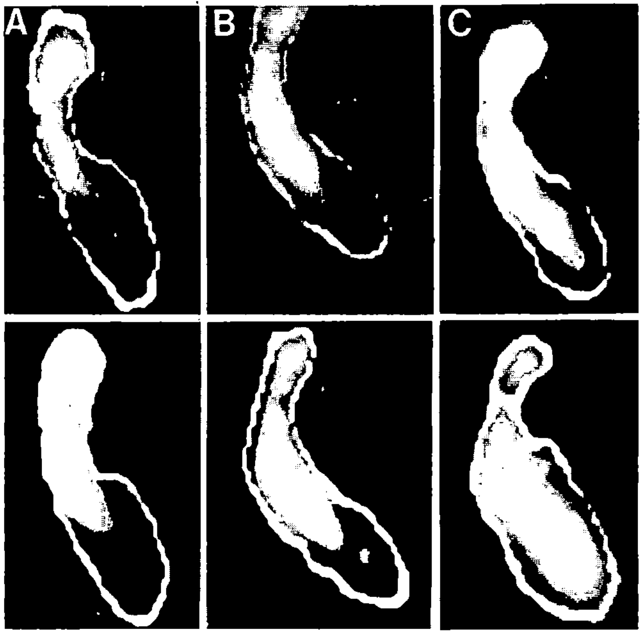


FIG. 8. These static left ventricular images were obtained at rest (top row) and exercise (bottom row) in a normal subject (A), patient with one vessel coronary artery disease (B), and a patient with left main and circumflex coronary artery stenosis (C). The outer border of each image represents the border of left ventricular end-diastolic outline and ascending aorta. Within this border is the residual end-systolic tracer.

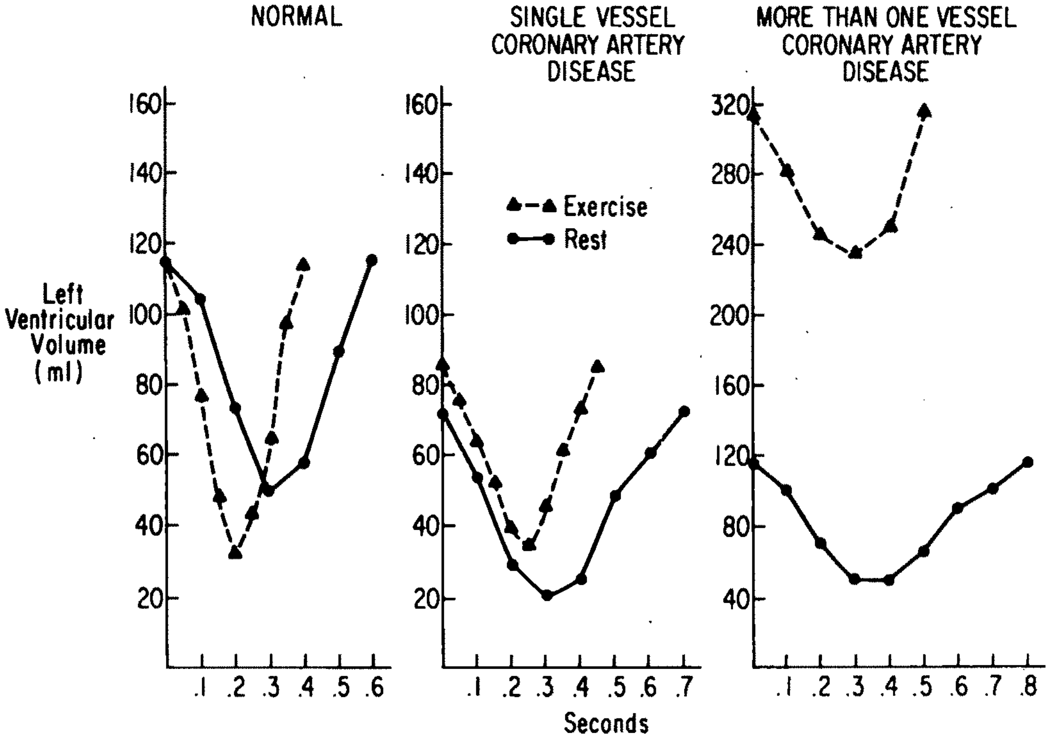


FIG. 9. Response to exercise. These left ventricular volume curves were obtained in the three patients illustrated in Figure 8. During exercise, end-diastolic volume is unchanged in the normal and end-systolic volume is decreased. In patients with one vessel and more than one vessel coronary artery disease, a progressive increase in end-diastolic and systolic volumes is observed.

changes are not caused solely by differences in left ventricular after-load in the three groups. The data describing left ventricular function during exercise clearly separate the three groups.

Discussion

In a study of the linear velocity of blood flow in 1927, Blumgart and Yens introduced the use of radioactive tracers in clinical cardiology.[2,3] In 1949, Prinzmetal and associates recorded passage of radioactivity through the heart using a Geiger counter and analyzed quantitative differences produced by circulatory abnormalities.[24] Use of a nondiffusible radioactive tracer by Shipley and colleagues permitted the determination of cardiac output without arterial sampling.[28] In 1957, Huff and coworkers used data obtained from four detectors over the chest to calculate central transit times and blood volume.[15] After these initial studies, widespread use of isotopes in clinical cardiology was predicted because of their innocuous nature. Inaccuracy, however, caused by difficulty in positioning detectors over a known cardiac region, limited routine application of these techniques. Refinement of instrumentation

TABLE 5. *Statistical Analysis Between Groups*

	Normal Ventricle vs. One Vessel Coronary Artery Disease		Normal Ventricle vs. More Than One Vessel Coronary Artery Disease		One Vessel Coronary Artery Disease vs. More Than One Vessel Coronary Artery Disease	
Hemodynamic Parameters	Rest	Exercise	Rest	Exercise	Rest	Exercise
Heart Rate (beats/min)	NS	↓<0.00002	NS	↓$<10^{-9}$	NS	NS
Mean Blood Pressure (mm/Hg)	NS	NS	NS	NS	NS	NS
Cardiac Index (L/min/m^2)	NS	↓<0.01	NS	↓<0.00002	NS	NS
Ejection Fraction (%)	NS	↓<0.00002	NS	↓$<10^{-9}$	NS	↓<0.0002
Left Ventricular End-Diastolic Index (ml/m^2)	NS	NS	NS	↑$<10^{-8}$	↑<0.05	↑<0.001
Left Ventricular Stroke Volume Index (ml/m^2)	NS	NS	NS	NS	NS	NS
Left Ventricular End-Systolic Volume (ml/m^2)	NS	↑<0.00002	↑<0.05	↑$<10^{-9}$	NS	↑<0.003
Pulmonary Blood Volume Index (ml/m^2)	NS	NS	NS	NS	NS	NS

NS Not statistically significant, ↓ significant decrease, ↑ significant increase, statistical significance < 0.05.

for rapid imaging and quantitation of radioactivity over a large area has renewed interest in radionuclide angiocardiography. Initial studies with these camera-like detectors provided a sequential pictorial display of the intracardiac passage of radionuclides.[11,18,20] Other studies have quantitated regional changes in radioactivity over the heart.[23] The results of these and similar studies suggest a variety of useful clinical applications of these techniques, particularly in patients with coronary artery disease.

The experimental design of the present study consists of an initial passage of tracer through the central circulation, a method commonly called the *first-pass technique*. Although multigated studies using equilibration of technetium human serum albumin within the circulation have been the most popular method of evaluating left ventricular function at rest and during exercise,[4,31,34] it is felt that the first-pass technique provides a broader understanding of changes in chamber volume within the entire central circulation. In addition, since all previous noninvasive studies have been performed in the supine position, the technique of first-pass study has enabled the performance of measurements in the more natural erect position at rest and during exercise. In this study, exercise data were obtained prior to the resting study. This was done to alleviate the problem of subtracting background counts during exercise. Adequate recovery times from ten to 30 minutes were allowed in which heart rate, blood pressure, and electrocardiographic tracings returned to pre-exercise levels, assuring reliable left ventricular hemodynamic values at rest.

The effects of exercise upon the central circulation in normal erect human subjects have been studied by numerous investigators during the past two decades. Augmentation of cardiac output with exercise has been shown to result from a large increase in heart rate and a moderate increase in stroke volume.[1,6,8,12,13,21] Remarkable left ventricular hemodynamics can be achieved in well conditioned athletes. An extraordinary example of cardiac performance was observed in a college athlete at maximal exercise to exhaustion (Table 6). This study simply illustrates the extremes of left ventricular function at which man is able to perform.

Data obtained in the present studies in controls (Group I) revealed that augmentation of cardiac output from rest to exercise resulted primarily from a 110% increase in heart rate. Moreover, a 34% increase in stroke volume contributed to the increase in cardiac output during exercise. The stroke volume increased with exercise in the erect position more than the end-diastolic volume, which caused an increase in left ventricular ejection fraction. Therefore, the end-systolic volume decreased significantly from rest to exercise. The increase in cardiac output greatly decreased the pulmonary transit time, and the pulmonary blood volume increased with maximal exercise in the group of normal subjects, but large individual variation was observed.

TABLE 6. *Cardiac Performance in a 22-Year-Old Varsity Collegiate Swimmer*

	Rest	Exercise
Heart rate (beats/min)	51	210
Blood pressure (mm/Hg)	112/74	182/68
Ejection fraction (%)	74	97
End-diastolic volume (ml)	201	278
End-systolic volume (ml)	52	8
Stroke volume (ml)	149	270
Cardiac output (L/min)	7.6	56.6

A comparison of left ventricular hemodynamic parameters measured in a world-class college athlete after six months of intensive training. These data suggest that cardiac output at maximal exercise results from an extreme increase in heart rate associated with a large increase in end-diastolic volume. Moreover, augmentation of myocardial contractility (ejection fraction) is enhanced, which results in an 8 ml residual at end-systole. This study was taken from unpublished data determining the effects of intensive training upon the central circulation in 18 college athletes.

In the ten patients with documented single vessel coronary artery disease (Group II), two patients had prior myocardial infarction. Patient 7 had a negative adequate treadmill test, while Patient 9 had a negative inadequate test. In both patients, abnormal wall motion studies at catheterization were also documented at rest during the radionuclide study. Furthermore, during the course of the exercise study, no areas of abnormal wall motion were noted. A 115% increase in cardiac output occurred with a 51% increase in heart rate and a 39% increase in stroke volume. In this group, both the end-diastolic and end-systolic volume increased during exercise, resulting in no significant change in ejection fraction from rest to exercise. The failure to increase left ventricular ejection fraction and the increase in end-systolic volume with exercise provided clear separation between Groups I and II. Therefore it becomes apparent tha, in patients with one vessel disease, maintenance of cardiac output and stroke volume requires an increase in end-diastolic volume and heart rate. This demonstrates the early manifestation of cardiac dilatation (Frank-Starling relationship), which serves as a protective mechanism for preservation of cardiac output.

Wall motion appeared normal at rest in nine of ten patients in Group II evaluated by radionuclide scans. However, in four of ten patients, exercise-induced ischemia produced segmental wall abnormalities which were not apparent at rest. This observation has also been documentd by other investigators.[4,9,27] Furthermore, prior stress treadmill electrocardiograms in five of the ten patients were either negative inadequate, negative adequate, or in one patient uninterpretable secondary to pre-existing electrocardiographic changes. Although the numbers are small in this group, it appears that exercise radionuclide angiocardiography may be more sensitive in selecting those patients with ischemic myocardium compared to those who have had prior myocardial infarctions and no ischemia.

Patients in Group III attained a 98% increase in cardiac output by a 59% increase in heart rate and a 21% increase in stroke volume. However, the increase in stroke volume required a large increase in left ventricular volume. The end-diastolic volume increased 57% to an average of 216 ml, and the end-systolic volume increased 94% to an average of 120 ml. Although the stroke volume increased, the ejection fraction decreased from rest to exercise because of the increase in end-diastolic volume. Therefore, stroke volume is preserved by extremely large increases in end-diastolic volume with resultant acute cardiac dilatation. This emphasizes the importance of pre-load (Frank-Starling mechanism) as a basis for preservation of left ventricular function during exercise. Intercomparison among Groups I through III illustrates several important points (Table 5). Mean blood pressure was not statistically significant. Although this measurement was obtained peripherally, it implies that observed left ventricular dysfunction seen at exercise was not on the basis of increased after-load. As the extent of vessels involved with coronary artery disease increases, myocardial contractility decreases with exercise. Moreover, in order to maintain stroke volume and cardiac output, large increases in end-diastolic volume and end-systolic volume occur. A clear separation was observed among the three groups (Table 5), on the basis of ejection fraction, end-diastolic volume, and end-systolic volume.

Although pulmonary blood volume increased from rest to exercise in each group (Figs. 1–3), there was no statistical difference among the groups (Table 5). Consequently, it is felt that pulmonary blood volume analysis is of limited value as a predictor of ischemic coronary artery disease.

Braunwald and associates, as well as other investigators, have shown that increased cardiac output induced by exercise in normal man is a result of increased heart rate. This has been referred to as the "masking effect" of the Frank-Starling mechanism produced by exercise tachycardia. This effect is further supported by the fact that fixed atrial pacing during exercise in experimental animals and normal subjects demonstrates an increase in end-diastolic dimensions of the left ventricle.[8,14,19,29,30,32,33] The present data support those of previous investigators showing an increase in stroke volume from rest to exercise in erect man. Furthermore, the data also illustrate that there is a slight increase in end-diastolic volume in erect man at exercise. In patients with induced ischemic coronary artery disease during exercise, acute cardiac dilatation was observed. Sharma and associates also noted this dilatation in exercising patients with coronary artery disease with a greater increase in end-diastolic volume than stroke volume causing a decrease in ejection fraction.[27] The Frank-Starling mechanism is clearly important in the preservation of stroke volume in patients with ischemic coronary artery disease with an increase in cardiac output induced by exercise.

In summary, resting and exercise radionuclide angiocardiography affords a unique and thorough evaluation of left ventricular hemodynamic parameters in patients with coronary artery disease. These studies also demonstrate that the use of radionuclide angiocardiograms at rest and during exercise may prove a valuable adjunct to the screening of patients with chest pain. Moreover, the technique permits a meaningful prognosis to be made and it is also of value in establishing the diagnosis and in objective follow-up of patients with myocardial ischemia.

References

1. Bevegard, S., Holmgren, A. and Jonsson, B.: The Effect of Body Position on the Circulation at Rest and During Exercise, with Special Reference to the Influence on the Stroke Volume. Acta Physiol. Scand., 49:279, 1960.
2. Blumgart, H. L., and Yens, O. C.: Studies in the Velocity of Blood Flow. I. The Method Utilized. J. Clin. Invest., 4:11, 1927.
3. Blumgart, H. L. and Weiss, S.: Studies in the Velocity of Blood Flow. VII. The Pulmonary Circulation Time in Normal Resting Individuals. J. Clin. Invest., 4:399, 1927.
4. Borer, J. S., Bacharach, S. L., Green, M. V., et al.: Real-time Radionuclide Cineangiography in the Non-invasive Evaluation of Global and Regional Left Ventricular Function at Rest and During Exercise in Patients with Coronary Artery Disease. N. Engl. J. Med., 296:839, 1977.
5. Bruce, R. A.: Exercise Testing of Patients with Coronary Heart Disease. Ann. Clin. Res., 3:323, 1971.
6. Chapman, C. B., Fisher, J. N. and Sproule, B. J.: Behavior of Stroke Volume at Rest and During Exercise in Human Beings. J. Clin. Invest., 30:1208, 1960.
7. Dodge, H. T., Hay, R. E. and Sandler, H.: An Angiocardiographic Method for Directly Determining Left Ventricular Stroke Volume in Man. Circ. Res., 11:739, 1962.
8. Epstein, S. E., Robinson, B. F., Kahler, R. L. and Braunwald, E.: Effects of Beta-adrenergic Blockage on Cardiac Response to Maximal and Submaximal Exercise in Man. J. Clin. Invest., 44:1745, 1965.
9. Eubanks, D. R., Tsakiris, A. G., Davis, G. D., et al.: Left Ventricular Volumes During Exercise-induced Angina in Patients with Coronary Artery Disease. Circulation, 42(Suppl. 3:111, 1970.
10. Geddes, M. E.: The indirect measurement of blood pressure in man. *In* The Direct and Indirect Measurement of Blood Pressure. Chicago, Year Book Medical Publishers, Inc., 1970, p. 70.
11. Graham, T. P., Goodrich, J. K., Robinson, A. E., et al.: Scinti-

angiocardiography in Children. Rapid Sequence Visualization of the Heart and Great Vessels After Intravenous Injection of Radionuclide. Am. J. Cardiol., 25:387, 1970.

12. Guyton, A. C., Jones, C. E. and Coleman, T. G.: Cardiac output in muscular exercise. *In* Circulatory Physiology: Cardiac Output and its Regulation. Philadelphia, W. B. Saunders Co., 1973, p. 436.
13. Holmgren, A. and Ovenfors, C. O.: Heart Volume at Rest and During Muscular Work in the Supine and in the Sitting Position. Acta Med. Scand., 167:267, 1960.
14. Horwitz, L. D., Atkins, J. M. and Leshin, S. J.: Role of the Frank-Starling Mechanism in Exercise. Circ. Res., 31:868, 1972.
15. Huff, R. L., Parrish, D. and Crockett, W.: A Study of Circulatory Dynamics by Means of Crystal Radiation Detectors on the Anterior Thoracic Wall. Circ. Res., 5:395, 1957.
16. Jones, R. H., Goodrich, J. K. and Sabiston, D. C., Jr.: Quantitative Radionuclide Angiocardiography in Evaluation of Cardiac Function. Surg. Forum, 22:128, 1971.
17. Jones, R. H. and Scholz, P. M.: Data enhancement techniques for radionuclide cardiac studies. *In* Medical Radionuclide Imaging, vol. 2. Vienna, International Atomic Energy Agency, 1977.
18. Kriss, J. P., Enright, L. P., Hayden, W. G., et al.: Radioisotopic Angiocardiography. Wide Scope of Applicability in Diagnosis and Evaluation of Therapy in Disease of the Heart and Great Vessels. Circulation, 43:792, 1971.
19. Liljestrand, G., Lysholm, E. and Nylin, E.: Immediate Effects of Muscular Work in the Stroke and Heart Volume in Man. Scand. Arch. Physiol., 80:265, 1938.
20. Mason, D. T., Ashburn, W. L., Harbet, J. C., et al.: Rapid Sequential Visualization of the Heart and Great Vessels in Man Using the Wide-field Anger Scintillation Camera. Radioisotope-angiography Following Injection of Technetium-99m. Circulation, 59:19, 1969.
21. Mitchell, J. H., Sproule, B. J. and Chapman, C. B.: The Physiological Meaning of the Maximal Oxygen Intake Test. J. Clin. Invest., 37:538, 1958.
22. Peterson, K.: Improved Diagnosis of Coronary Artery Disease During Exercise Testing Using a Computer Processed Thallium-201 Image. Circulation, 54 (Suppl. 2):207, 1976.
23. Pierson, R. N., Jr., Kriss, J. P., Jones, R. H. and MacIntyre, W. J., eds.: Quantitative Nuclear Cardiography. New York, John Wiley and Sons, 1975.
24. Prinzmetal, M., Corday, E. Spritzler, R. H., et al.: Radiocardiography and its Clinical Applications. JAMA, 130:167, 1949.
25. Ritchie, J. L., et al.: Myocardial Imaging with Thallium-201 at Rest and During Exercise: Comparison with Coronary Arteriography and Resting and Stress Electrocardiography. Circulation, 56:66, 1977.
26. Rivas, F., Cobb, F. R., Bache, R. J. and Greenfield, J. C., Jr.: Relationship Between Blood Flow to Ischemic Regions and Extent of Myocardial Infarction. Circ. Res., 38:439, 1976.
27. Sharma, B., Goodwin, J. F., Raphael, M. J., et al.: Left Ventricular Angiography on Exercise: A New Method of Assessing Left Ventricular Function in Ischemic Heart Disease. Br. Heart J., 38:59, 1976.
28. Shipley, R. A., Clark, R. E., Leibowitz, D., et al.: Analyses of Radiocardiogram and Heart Failure. Circ. Res., 1:428, 1953.
29. Starling, E. H.: The Linacre Lecture on the Law of the Heart. Given at Cambridge, 1915. London, Longmans, 1918.
30. Starling, E. H.: On the Circulatory Changes Associated with Exercise. J. R. Army Med. Corps, 34:258, 1920.
31. Strauss, H. W., Zaret, B. L., Hurley, P. J., et al.: A Scintiphotographic Method for Measuring Left Ventricular Ejection Fraction in Man without Cardiac Catheterization. Am. J. Cardiol., 28:575, 1971.
32. Vatner, S. F. and Pagani, M.: Cardiovascular Adjustments to Exercise: Hemodynamics and Mechanisms. Prog. Cardiovasc. Dis., 19(2):91, 1976.
33. Vatner, S. F., Franklin, D., Higgins, C. B., et al.: Left Ventricular Response to Severe Exertion in Untethered Dogs. J. Clin. Invest., 51:3052, 1972.
34. Zaret, B. L., Strauss, H. W., Hurley, P. J., et al.: A Noninvasive Scintiphotographic Method for Detecting Regional Ventricular Dysfunction in Man. N. Engl. J. Med., 284:1165, 1971.
35. Zaret, B. L., Strauss, H. W., Martin, N. D., et al.: Non-invasive Assessment of Regional Myocardial Perfusion with Potassium 43 at Rest, Exercise, and During Angina Pectoris. Circulation, 46 (Suppl. 2):11, 1972.

DISCUSSION

DR. FRANK C. SPENCER (New York, New York): To those of you who are not familiar with the field, it should be emphasized that this probably represents the best data in the world on the measurement of cardiac function in the ambulatory patient by noninvasive techniques. It is typical of the kind of scholarly presentation we have come to expect from Duke. Similarly, it is a tribute to Dr. Sabiston's leadership in guiding young men into basic investigation that produces work of this quality.

The physiologic fact that in trained olympic swimmers, the cardiac output may momentarily exceed 50 liters is quite significant in itself. A widespread clinical application of the technique is that it may permit the noninvasive measurement of cardiac function before and after different types of cardiac operations.

A popular subject on both television and the newspapers is the influence of coronary bypass on longevity and whether the benefit is worth the cost. As President Scott has emphasized, this has been quickly seized upon by so-called "health planners" with their over-zealous efforts at regulation. A truism with any operation is that it should benefit function more than it harms. With coronary bypass, the question is whether the increase in blood flow to ischemic heart muscle outweights the possible harm from the operative procedure. What has been missing to date is a simple way of measuring cardiac function both before and after operation by a noninvasive technique, rather than our existing methods of the complex cardiac catheterization, which is both time consuming, expensive, and often not possible because the patient feels well and does not wish to undergo catheterization.

A screening test like this one has great potential. Note the remarkable study of ejection fraction with coronary disease, with the example of the ejection fraction decreasing from 0.74 to 0.26 with exercise. One can imagine the possible harm, or even death, that could result from a patient like this undertaking unsupervised jogging.

To emphasize the importance of the coronary bypass question even further, the fact that coronary disease is the leading cause of death in the Caucasian male throughout the world, including New Zealand, Australia, U.S.A., England, and Finland, is a crucial fact. A recent world-wide study has found the frequency of coronary disease in middle-aged U.S. males to be about 8%, certainly, an extremely common problem.

Our data at New York University with coronary bypass reported at the American Thoracic Association Meeting last April strongly indicate a great improvement in longevity in our experience with over 1100 patients in the past 7 years. These data, appearing in print soon, demonstrate a survival of 88% at 5 years, including the average operative mortality, and the survival curve is virtually identical to that of the normal population. With screening tests as shown in this publication, decisions can be reached much more quickly, rather than the time consuming method of evaluating the beneficial effects over a period of several years in randomized studies.

So, I closing, I would like to ask Drs. Jones and Sabiston two questions: Can this technique become cost effective and applicable in many hospitals? If so, can the quantitation that was demonstrated with the varsity swimmer be applied in many forms of heart disease treated with either medicine or surgery?

Thank you very much.

DR. STEPHEN K. RERYCH (Closing discussion): Cost effectiveness is a very important concern to the medical profession and it should be. Our procedure costs approximately $140.00 per study compared with $900.00 associated with the catheterization procedure. It can be done on an outpatient basis and requires very little time to perform and process the data. We feel, as do our cardiologists at Duke University, that the study at rest and exercise provides an effective means of screening patients with ischemic coronary artery disease. In addition, it may provide a more rational approach based on functional impairment of the left ventricle in determining which patients should continue with medical therapy and which patients should be brought to saphenous vein bypass grafting.

If I may, I would like to present a short film summarizing the technique of radionuclide angiocardiography. (A motion picture film was started.)

The first sequence, you will see, appears in a normal subject. Tracer is seen in the superior vena cava, right atrium, and right ventricle. As the tracer is ejected out the pulmonary artery, we now see blood flow to the right and left lung. The initial bolus now returns to the left atrium and ventricle, and is ejected out into the ascending aorta. This is normal ejection.

The film is repeated. Again, you will notice blood flow through the superior vena cava, right atrium, right ventricle, and pulmonary outflow tract. Tracer now appears in the right and left lung fields. It returns to the left atrium and ventricle and is ejected into the aorta.

The following two ventriculograms depict the comparison between a normal patient and a patient with diffuse coronary artery disease. These are resting studies. On your left, the normal patient demonstrates normal left ventricular emptying of tracer. In contrast, the patient on the right demonstrates abnormal ejection of tracer from the left ventricle into the aorta.

The next film sequence demonstrates a patient with a left ventricular aneurysm. The preoperative study on your left reveals abnormal global left ventricular wall motion. In addition, an area of paradoxical motion is seen over the anterior wall typical of an aneurysm. The postoperative study indicates effective cardiac ejection. This study illustrates the value of radionuclide angiocardiography as a screening tool to the surgical patient in the postoperative follow-up period.

The next study illustrates the dynamic effects of exercise with this radionuclide technique. On your right is a real-time cine of the transmit of tracer through the central circulation with the lung phase seen here at exercise. Notice the normal vigorous left ventricular contractions. In contrast, the rest study on your left reveals the slow transit of tracer through the central circulation and the lungs seen here. The left ventricular contractility is normal but not nearly as vigorous as in the exercise study.

A repeat of the study again demonstrates these two physiological states.

The last study indicates the abnormal response to exercise seen in patients with ischemic coronary artery disease. On your left is the resting image. Note the normal left ventricular wall motion and ejection of tracer from the left ventricle into the aorta. On the other hand, at a heart rate of 120 beats per minute, abnormal wall motion is seen, and there is sluggish ejection of tracer from the left ventricle.

QUESTION: Dr. Scott, does that $140.00 pay for the machine?

DR. RERYCH: No sir. The machine is quite expensive. However, within a year, patient charges could offset the expense of instrumentation.

SAME SPEAKER: How much does the machine cost?

PRESIDENT SCOTT: Come on out, Dr. Rerych. There may be many questions.

DR. RERYCH: The machine costs $150,000. That is expensive hardware. However, when one includes all of the equipment in our laboratory, I would estimate the total cost at one quarter of a million dollars.

PRESIDENT SCOTT: Are there other questions?

QUESTION: What was that athlete doing when he measured 56l.?

DR. RERYCH: That was certainly an amazing study. I'm very fortunate to have a good rapport with the athletes I have studied. This is important if you want maximum performance. He is, as you noticed on the slide, a Silver Medalist in the Olympic Games. He is also a cyclist by hobby. Within the last minute of the exercise study prior to injection, he covered well over a kilometer on the bicycle at a very high workload. The amount of effort and energy was truly remarkable. In fact I could not believe the hemodynamic values we obtained; however, it is not impossible to explain these values since his performance as an athlete speaks for itself. In addition he exercised on the bicycle as if he were in a swimming race. In other words, he paced himself appropriately and gave his maximum effort at exactly the time I injected him which was ten minutes into the study.

PRESIDENT SCOTT: Other questions?

QUESTION: Are these programmed to any computer, or do you need a special computer?

DR. RERYCH: We use the Baird Atomic System 77 which employs a Nova 1230 computer with its own machine language. Consequently we are relegated to that particular computer model.

PRESIDENT SCOTT: Are there other questions? State your name, will you, so that we can get this in the record. (There were none.)

sterile

Micro-touch*

latex surgeons' gloves

The Problem Solvers...
put all the pieces together

- Consistent Quality • Consistent Performance
- Consistent availability through local dealer inventory

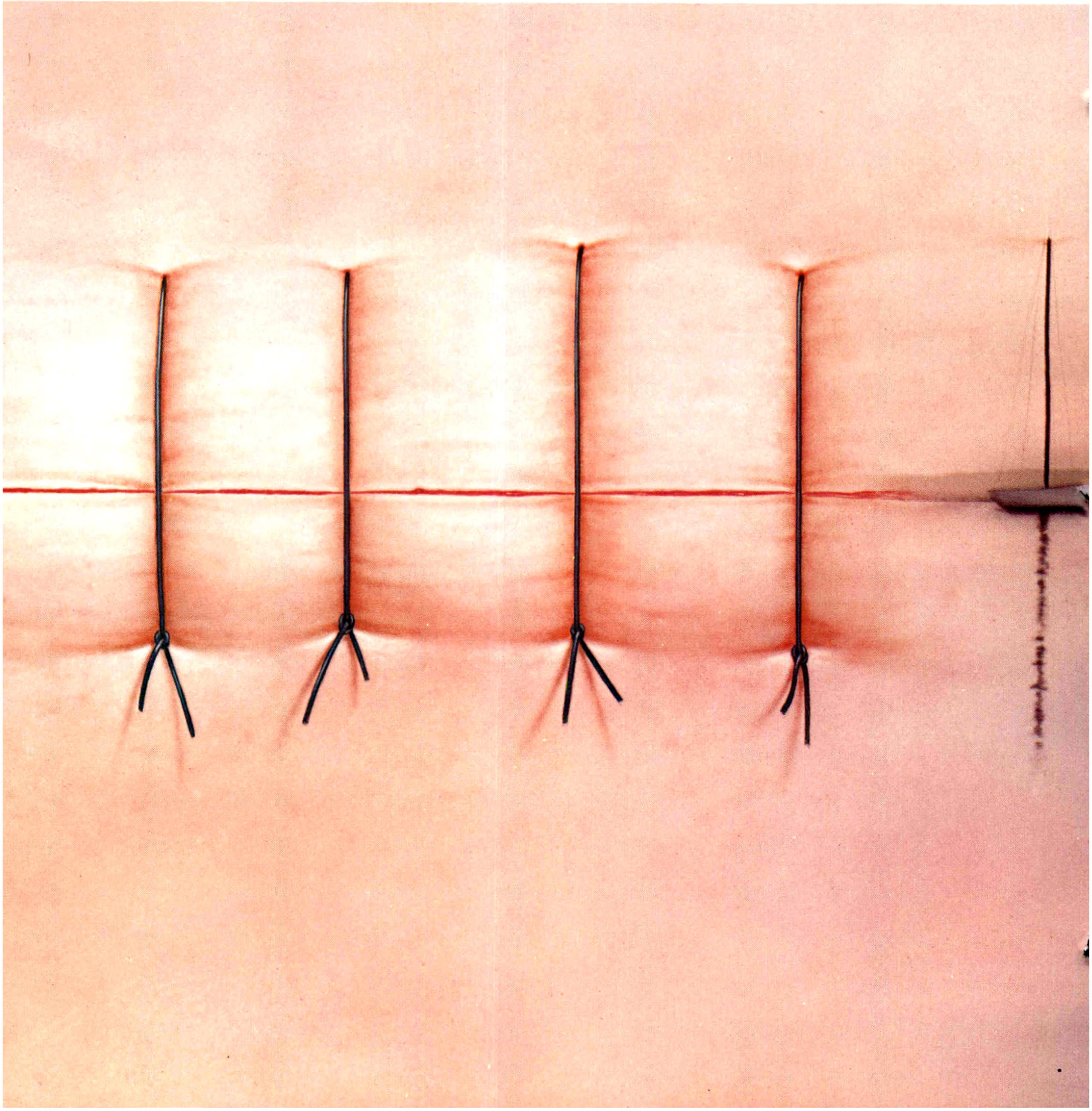
Arbrook*.

Arbrook, Inc., Arlington Texas 76010

"...it has long been recognized that anxiety, tension, agitation, and apprehension are all capable of increasing pain perception..."

Halpern, L. M.: Anxiety and pain in postoperative patients. Hospital Practice *(special report) January 1977, pp 31-*

Following surgery... the perception of pain diminished



Vistaril® I.M.
(hydroxyzine HCl)

by Calm

- reduces the anxiety component of pain
- permits reduction in narcotic dosage
- controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

© 1977, Pfizer Inc.

Vistaril® I.M.
(hydroxyzine HCl)
100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

preoperatively and postoperatively

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY
VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only
Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

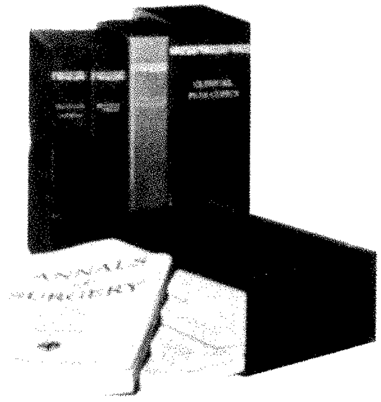
Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.
Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.
Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.
Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml—10 ml vials; 50 mg/ml—2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml—1 ml fill; 100 mg/2 ml—2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

Pfizer
LABORATORIES DIVISION
PFIZER INC



PRESERVE and PROTECT YOUR COPIES OF ANNALS of SURGERY

Now, your journals can become a handsome addition to your professional library.

These file boxes are designed and custom-made to keep your copies orderly, readily accessible and clean.

Durable book-binder's board covered with scuff-resistant, washable Leathertex. Lettering embossed in 23-Karat gold leaf.

Jesse Jones Box Corp. (since 1843)
Dep't. JBLA—Phila., Pa. 19141

Gentlemen: Kindly send me:
Reasonably priced, too. Only $4.95 ea. ☐
3 for $14.00 ☐ 6 for $24.00 ☐

Add $1.00 postage per file for orders outside the U.S.

☐ Check enclosed (Make check payable to: Jesse Jones Box Corp., Box 5120, Phila., Pa. 19141)

Name ______________________
Address ______________________
City/State/Zip ______________________

Shipped postpaid U.S. only. Satisfaction unconditionally guaranteed or your money back.

PROBLEM

SURGICAL PATIENTS WHO ARRIVE IN THE O.R. WITH NICKS AND CUTS DUE TO RAZOR PREPPING

SOLUTION

SURGEX THE NUMBER ONE DEPILATORY HOSPITALS HAVE BEEN USING FOR YEARS.

THE AORN STATES THAT A DEPILATORY SHOULD BE USED WHENEVER POSSIBLE.*

SOME OTHER ADVANTAGES **SURGEX** HAS OVER A RAZOR:

- **LESS SKIN SURFACE BACTERIA.*** Visible and microscopic skin injuries by a razor provide access for pathogenic organisms normally present on the skin.
- **EXCELLENT FOR USE ON EXTREMITIES.** SURGEX is known for its effectiveness, particularly when applied to bony contoured areas that are difficult to shave.
- **PREPS CAN BE DONE ONE DAY PREOPERATIVELY.** If razor prepping is performed more than a few hours before surgery, the minor abrasions produced provide a good culture medium. This necessitates shaving be done immediately before surgery. This is not necessary with SURGEX because there are no abrasions.
- **LONGER LASTING.** SURGEX removes hair below the skin line.
- **ELIMINATES PATIENTS' APPREHENSION OF A RAZOR.** With SURGEX, patients are more relaxed. They can actually apply it themselves in some cases.

For further information and possible in-service, please call (toll free) 800-225-3238, Ron Metro, **SURGEX** Product Manager. In Massachusetts call 923-1720.

COOPER SCIENTIFIC CORPORATION
372 Main Street
Watertown, Massachusetts 02172

*

REF: AORN JOURNAL, May 1976. Vol. 23, No. 6, Pg. 974-975.

Seropian, R., Reynolds, B.M.: Wound infections alter Preoperative Depilatory versus Razor Preparation: Am. Journal of Surgery, Vol. 121, March, 1971.

Powis, S.J.A., et al. Preoperative skin preparation: Clinical evaluation of depilatory cream: British Medical Journal, Vol. 2, November 1976.

☐ I am interested in evaluating SURGEX for our hospital.

☐ If it is possible to have an in-service in my area please contact me in reference to arranging one.

NAME ____________________

DEPT. ____________________

HOSPITAL ____________________

ADDRESS ____________________

CITY __________ *STATE* ______ *ZIP* ______

PHONE __________ *A/C* __________

When did you last hear 'rave reviews'- for an intraperitoneal irrigation agent?

"We were satisfied that kanamycin was not only safe, but also effective in improving survival in the presence of peritoneal contamination." —Nelson, J.L., et al.: Symposium on Surgical Infections and Antibiotics, Surg. Clin. of N.A. 55:6, pages 1391-1395, (December) 1975.

"Kanamycin has been employed in 128 patients at the time of operation for intraperitoneal contamination of various types. There has been no evidence of toxicity from this use of kanamycin." —Cohn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

"Wider usage of intraperitoneal kanamycin is advocated when intraperitoneal antibiotic therapy is indicated." —Cohn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

"...immediate operative use of intraperitoneal antibiotic treatment has lowered the incidence of complications and mortality by 42%." —Clowes, G.H.A.: Forum on Peritonitis, Mod. Med. 40:153 (Apr. 17) 1972.

...our choice at the operating table is kanamycin..." —Clowes, G.H.A.: Forum on Peritonitis, Mod. Med. 40:153 (Apr. 17) 1972.

"Intraperitoneal kanamycin therapy is strongly advocated for any patient with peritonitis." —DiVicenti, F.C., and Cohn, I., Jr.: Am. Journ. Surg. 111:1, pages 147-153, (June) 1965.

"In peritonitis, intraperitoneal administration of kanamycin can be recommended..." —Pissiotis, C.A., et al.: Surg. Gynecol. Obstet. 134:995 (June) 1972.

Kantrex®

KANAMYCIN SULFATE

a known quantity

BRISTOL™
BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Kantrex® Injection
and Pediatric Injection
(kanamycin sulfate injection)
(13) 2/28/78

For complete information, consult Official Package Circular.

WARNING:
The major toxic effect of parenterally administered kanamycin sulfate is its action on the auditory portion of the eighth nerve. High frequency deafness usually occurs first and can be detected by audiometric testing. Tinnitus or vertigo may occur and are evidence of vestibular injury and impending bilateral irreversible deafness.

In patients with impaired kidney function, the risk of severe ototoxic reactions and permanent deafness is sharply increased. In such cases, the daily dosage should be reduced and the interval between doses lengthened. If there is evidence of progressive renal dysfunction (increasing NPN, BUN, creatinine or oliguria) during therapy, audiometric tests are advised and discontinuation of the drug should be considered.

Older patients and patients receiving a total dose of more than 15 Gm. of kanamycin sulfate should be carefully observed for signs of eighth nerve damage.

Infants and children generally tolerate the drug well; and when the recommended precautions are followed, the incidence of toxic reactions is low.

Neuromuscular paralysis with respiratory depression may occur when kanamycin sulfate is administered intraperitoneally concomitantly with anesthesia and muscle-relaxing drugs. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug.

The concurrent systemic use of other ototoxic and/or nephrotoxic drugs, particularly streptomycin, polymyxin B, polymyxin E (colistin), neomycin, gentamicin, and viomycin should be avoided.

The administration of kanamycin sulfate and rapid acting diuretic agents, e.g. ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, and mannitol (particularly when the diuretic is given intravenously) may cause irreversible deafness. Concurrent use of these agents should be avoided. (See "Adverse Reactions".)

Usage in Pregnancy
Safety of this drug in human pregnancy has not been established.

CONTRAINDICATIONS:
A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other potentially ototoxic agents may be a contraindication if effective, alternative therapy is available.

THIS DRUG IS **NOT** INDICATED IN LONG-TERM THERAPY (e.g. Tuberculosis) BECAUSE OF THE OTOTOXIC HAZARD WITH EXTENDED ADMINISTRATION.

WARNING:
See "Warning" box above.

PRECAUTIONS:
Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occurs, discontinue therapy. Mycotic or bacterial superinfection may occur.

ADVERSE REACTIONS:
Nephrotoxicity — albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity — see box warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

DOSAGE AND ADMINISTRATION:
The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult total daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gm.

The intravenous route is used only if intramuscular administration is not feasible. The 500 mg. dose is added to the 200 ml. of sterile diluent and administered 60 to 80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

As aerosol treatment, 250 mg. of Kantrex is diluted with 3 ml. of physiological saline and nebulize.

Kantrex Injection in concentrations of 0.25 per cent (2.5 mg./ml.) has been used satisfactorily as an irrigating solution in abscess cavities, pleural spaces, peritoneal and ventricular cavities.

SUPPLIED:
Rubber capped vials as a ready-to-use sterile aqueous solution in two concentrations:
KANTREX INJECTION (kanamycin sulfate injection)
  NDC 0015-3502-20 — 500 mg. per 2 ml.
  NDC 0015-3502-24 — Disposable Syringe (500 mg. per 2 ml.)
  NDC 0015-3503-20 — 1.0 Gm. per 3 ml.
KANTREX PEDIATRIC INJECTION (kanamycin sulfate injection)
  NDC 0015-3512-20 — 75 mg. per 2 ml.
(activity assayed as kanamycin base)

BRISTOL™ BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

ATLAS OF APPLIED VASCULAR SURGERY

■

By KIYOSHI INOKUCHI, M.D.,

and AKIRA KUSABA, M.D.

Here is a unique and timely atlas text describing the wide variety of diseases and lesions that have been successfully treated through vascular anastomoses performed with a new stapling instrument originated and perfected by Dr. Inokuchi.

The extensive experiences of the authors with vessel suturing equipment have extended the use of these instruments beyond the repair and reconstruction of vessels, to other areas of surgery. For example, use of the Inokuchi stapling instrument has made possible the free transplantation of intestine as a reconstruction of the cervical esophagus.

A highlight of the book is a discussion of the many problems and difficulties which arise in portacaval shunt for portal hypertension. The authors have realized success in this operation and describe a new technique—left gastric venous-caval shunt.

This highly descriptive book contains details on the design of the Inokuchi vascular stapler and step-by-step instructions on its use and applications. Many of the operations performed utilizing the device are discussed, describing the techniques used and giving case histories.

198 pages / 301 illustrations, including 68 photographs.
11 in color / 21 Tables / 1975 / $57.00.

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:
☐ ATLAS OF APPLIED
VASCULAR SURGERY $57.00
Name ______________________________
Address ____________________________
City ____________ State ________ Zip ________

☐ Payment enclosed
Save postage & handling
☐ Charge and bill me
Plus postage & handling

Also available at your medical bookstore

AS 5/78

When the need for injectables is over...help keep your patient free of opiates, relieve pain.

Potent - Dependable - Nonopiate

Talwin® HCl 50 mg.

brand of . equivalent to 50 mg. base

pentazocine HCl tablets, NF

Relieves pain as well as 60 mg. of codeine.

MILD ANALGESICS OFTEN DON'T WORK:

In a double-blind single dose study involving 225 adult inpatients, the comparative efficacy of 650 mg. aspirin, 65 mg. dextropropoxyphene, and 50 mg. pentazocine for relief of postoperative pain was recorded.[1]

- All patients were suffering from moderate or severe pain.
- Pregnant women as well as patients with known renal, respiratory, cardiac, or hepatic insufficiency were excluded.
- The onset of action of pentazocine was rapid.
- Although aspirin, dextropropoxyphene, and pentazocine produced significant relief from pain, pentazocine was significantly more effective at a half hour.
- Side effects were recorded for 16 patients: in the aspirin group 2 patients complained of drowsiness and 1 of dizziness. In the dextropropoxyphene group 5 patients vomited and 3 patients complained of drowsiness or dizziness, while 5 patients who had received pentazocine complained of dizziness.
- Pentazocine should be an oral analgesic of choice for treatment of postoperative pain.

Opiates are too addictive, too restrictive:

"Despite their potent analgesic action, the morphine-like analgesics have disadvantages that limit their usefulness: respiratory depression, nausea, vomiting, constipation, cardiovascular effects (hypotension, bradycardia), histamine release, and in some patients, an increase in intracranial pressure. Other adverse reactions include miosis, spasm of the biliary and urinary tracts, and rarely, hypersensitivity phenomena (urticaria, rash, and anaphylactic reactions). Frequent repeated use produces psychic and physical dependence."[2]

Oral Talwin shows infrequent occurrence of certain adverse effects as:

- Severe respiratory depression
- Hypotension
- Constipation
- Urinary retention
- Tachycardia

Among RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions—hallucinations (usually visual)—have cleared spontaneously within a period of hours. Withdrawal symptoms after prolonged use of Talwin for the relief of pain have rarely been reported, even when administration was abruptly discontinued. There have been a few reports of dependence with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

For Continuing Postsurgical Pain Control

Talwin® HCl 50 mg.

brand of . equivalent to 50 mg. base

pentazocine HCl tablets, NF

1 or 2 tablets every three or four hours

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Nonopiate

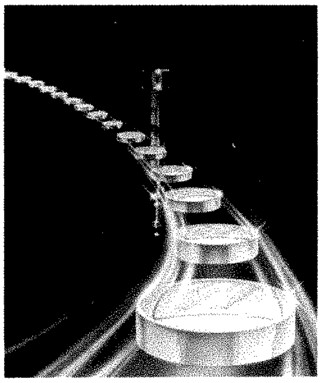
Talwin® HCl 50 mg.

brand of . equivalent to 50 mg. base

pentazocine HCl tablets, NF

Relieves pain of a moderate to severe nature.

Usual initial adult dose is 1 tablet every 3 or 4 hours.



Please consult full prescribing information before prescribing. A summary follows:
Talwin HCl is intended for the relief of moderate to severe pain. One 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. Talwin is a weak narcotic antagonist with sedative activity.

Contraindication
Hypersensitivity to pentazocine.

Warnings
Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin HCl should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions
Oral Talwin has been rarely reported to cause respiratory depression. It should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

Adverse Reactions
Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations; and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, paresthesia, toxic epidermal necrolysis.

Dosage and Administration
Adults: The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg. Tolerance is rare. Abrupt discontinuance following chronic use has rarely caused withdrawal symptoms.

Overdosage
Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

References

1. Kay B: A clinical comparison of orally administered aspirin, dextropropoxyphene and pentazocine in the treatment of postoperative pain. *J Int Med Res* 2:149-152, 1974.
2. AMA Department of Drugs: *AMA Drug Evaluations*, ed 3. Littleton, Mass, Publishing Sciences Group, Inc, 1977, pp 327-328.

3096

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

Cholecystosonography for the Diagnosis of Cholecystolithiasis

PETER J. DEMPSEY, M.D., JOSEPH F. PHILLIPS, M.D., DAVID L. WARREN, M.D., ARTHUR J. DONOVAN, M.D.

The gallbladder can be visualized by ultrasound (cholecystosonography) and gallstones seen as echo producing densities. Under cholecystosonographic observation the gallbladder can be demonstrated to contract following stimulation by cholecystokinin. This establishes patency of the cystic duct and excludes a diagnosis of acute obstructive cholecystopathy. The gallbladder has been identified in 84 of 86 patients. Stones have been identified sonographically in 64% of 42 patients with proven gallstones (75% of the last 20 cases). The gallbladder contracted following stimulation in 18 of 20 cases with a patent cystic duct. Cholecystosonography is simple, safe and economical. Cholecystosonography with cholecystokinin stimulation is the first diagnostic study to be performed when cholecystolithiasis is suspected and the following circumstances exists: a) an acute right upper quadrant (RUQ) syndrome consistant with acute obstructive cholecystopathy. b) cholestasis or hepatic dysfunction. c) a history of allergy to contrast media. Cholecystosonography may detect gallstones in a gallbladder visualized by oral cholangiography when stones are of the same density as the contrast media.

From the Departments of Radiology and Surgery, University of South Alabama College of Medicine, Mobile, Alabama

DIAGNOSTIC ULTRASOUND can image the gallbladder, identify stones present within the organ and document reduction in size following stimulation by a fatty meal or by cholecystokinin. This latter event establishes the patency of the cystic duct. This report will concern 86 cases in which gray scale cholecystosonography was employed in an attempt to identify cholecystolithiasis or, by demonstration of patency of the cystic duct, to exclude a diagnosis of obstructive cholecystopathy.

Method of Cholecystosonography

When possible, oral feeding is restricted for 12 hours. This is intended to permit distention of the gallbladder with bile. If an acute abdominal syndrome exists, a period of several hours of nasogastric suction prior to the examination is desirable to decompress the stomach and duodenum. Distention of the stomach and duodenum by fluid or air may interfere with visualization of the gallbladder. If a scan is technically unsatisfactory because of air in the stomach or duodenum, a repeat study after nasogastric emptying may permit a satisfactory examination. The examination can be performed without preparation. Under these circumstances, diagnostic reliability may be reduced.

A commercially available gray scale ultrasound machine is employed.* The transducers are either 2.25 or 3.5 mHz. A television screen displays the sonographic image and a permanent record is obtained using a multiformat camera system. The formerly employed B-mode depicted the outline of organs, whereas the newer gray scale depicts tissue interfaces in varying shades of gray. This permits imaging of parenchyma of organs.

To perform an abdominal examination by ultrasound a layer of mineral oil is placed on the abdomen. Multiple sonographic images are recorded in longitudinal, transverse and oblique planes during suspended respiration. The patient is placed in semi-upright and occasionally in the lateral decubitus right side up position and scanning is repeated in these positions. Gallstones are seen as echo producing densities in the gallbladder. The film employed to record the image of the gallbladder also records markings at 1 cm intervals at its periphery. These markings facilitate documentation of size of the

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

* Rohe Co., Santa Ana, California.

0003-4932-78-0500-0465-0105 © J. B. Lippincott Company

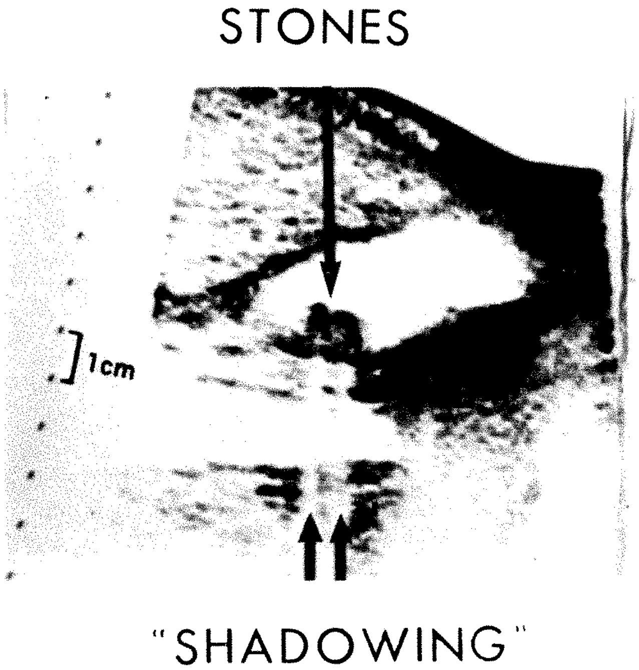


FIG. 1. A cholecystosonogram demonstrating echo producing densities created by gallstones. "Shadowing" is an area of reduced echo return due to attenuation of the ultrasound beam by the gallstones.

gallbladder. If gallstones are demonstrated, the examination is terminated.

In the absence of demonstrable gallstones, the gallbladder is stimulated. In some early cases this was accomplished by feeding of a fatty meal.† Since the spring of 1977, cholecystokinin‡ has been administered intravenously in a dose of 0.02 ugm/KBW. This synthetic hormone is the C-terminal octapeptide of cholecystokinin. Cholecystosonography is repeated at five minute intervals for up to 30 minutes thereafter to ascertain whether the gallbladder has changed in size. If reduction has occurred, the degree can be measured on the film. Cholecystokinin is reported to be more predictable than a fatty meal in producing reduction in size of the gallbladder.[10]

Criteria Employed for Cholecystosonographic Diagnosis

Criteria employed in this study to establish a diagnosis of cholecystolithiasis are three in number. One of the three must be present for a diagnosis of cholecystolithiasis. 1) Demonstration of echo producing densities in the structure established by anatomical position to be the gallbladder. These densities must be seen in at least two projections. 2) Acoustical "shadowing" shown in at least one projection to originate from the gallbladder. "Shadowing" is produced by attenuation of the ultrasound beam by gallstones and appears on the film as a band of reduced echo return. 3) Movement of the echoes interpreted as gallstones when the position of the patient is changed.

A cholecystosonogram demonstrating cholecystolithiasis and "shadowing" is depicted in Figure 1. Movement of stones within the gallbladder when the position of the patient is altered is depicted in Figure 2.

The sole criterion employed to establish patency of the cystic duct is reduction in size of the gallbladder following the administration of a fatty meal or cholecystokinin. A cholecystosonogram depicting reduction in size of the gallbladder following stimulation by cholecystokinin is depicted in Figure 3.

---

† Cholestrin.

‡ Kinevac, Squibb, Princeton, New Jersey.

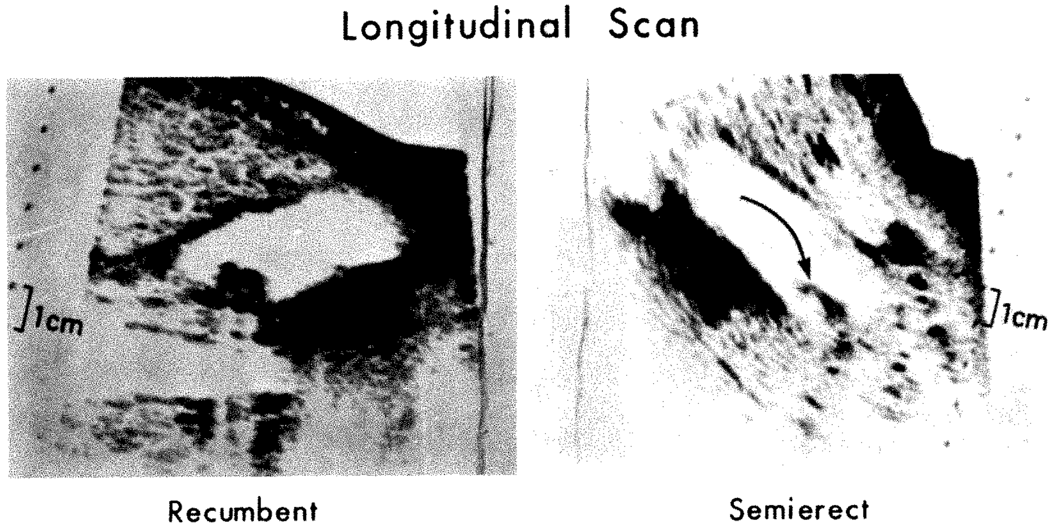


FIG. 2. A longitudinal scan demonstrating gallstones in the gallbladder which move into the fundus with a change from the supine to the semierect position.

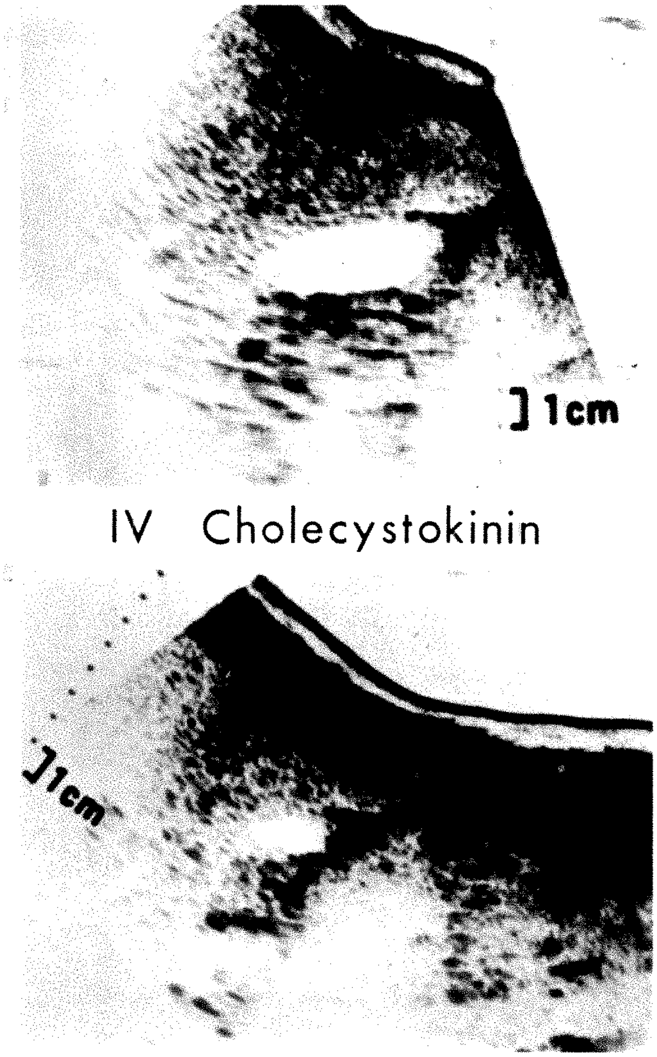


FIG. 3. After identification of the gallbladder as depicted in the upper cholecystosonogram, cholecystokinin was administered. The reduction in size of the gallbladder in the lower sonogram is apparent. Scale is identical in both sonograms.

Case Selection

Abdominal ultrasound has been performed at the University of South Alabama Medical Center on over 1000 cases between October of 1975 and October of 1977. In 108 of these cases the indication for abdominal ultrasound was either a suspicion of cholecystolithiasis or the same with obstructive cholecystopathy. The presence or absence of cholecystolithiasis was ultimately established in 86 of these 108 cases. This documentation was provided either by surgery or by cholangiographic visualization of the gallbladder—oral, intravenous, transhepatic or endoscopic and retrograde. Twenty-two cases in which the only basis for a final diagnosis was cholecystosonographic or clinical were excluded from further consideration.

Clinical Data

The indication for ultrasound in the 86 cases with proof of the presence or absence of gallstones can be divided into four categories.

Acute Right Upper Quadrant (RUQ) Syndrome—53 Cases

Cholecystosonography was performed because of suspicion of gallstone migration with acute obstructive cholecystopathy.

Cholestasis and Hepatic Dysfunction—11 Cases

In 11 cases with suspected cholecystolithiasis a laboratory pattern of cholestasis alone or together with hepatic dysfunction existed. Cholecystosonography was performed in an attempt to resolve the question of hepatocellular or lithiasic cause of the clinical disorder.

Confirmation of Oral Cholangiogram—21 Cases

Nonvisualization by oral cholecystogram—10 cases. In 10 cases the gallbladder had not been visualized by elective oral cholecystography and an inferential diagnosis of cholecystolithiasis had been made. Cholecystosonography was performed in an attempt to document the presence of gallstones.

Visualization by oral cholangiogram—11 cases. Cholecystosonography was performed in 11 cases despite prior cholangiographic visualization of the gallbladder. Dominant indications were "faint" cholangiographic visualization of the gallbladder, suspicion of stones, the possibility that stones were present which were the same density as the contrast media or a compulsive desire to confirm the cholangiographic diagnosis of gallstones.

Allergy to Iodine Containing Dye—1 Case

These indications for cholecystosonography are summarized in Table 1.

TABLE 1. *Cholecystosonography: Indications*

		No. Cases
Acute RUQ Syndrome		53
Cholestasis—Hepatic Dysfunction		11
Confirm Oral Cholangiogram		21
Nonvisualization	10	
Visualization	11	
Allergy to Contrast Media		1
		86

Table 2. *Cholecystosonography: Results—86 Cases*

	No. Cases
Gallbladder Visualized	84
Gallstones Present*	42
Sonographic Dx. 26/42 (64%)	
False Positive Dx. Gallstones	0

* Surgery or Cholangiogram.

Results

All Cases

The gallbladder was visualized in 84 of the 86 cases. Stones were ultimately proven to be present in the gallbladder in 42 of these cases. In 41 of the 42 cases with final proof of gallstones the gallbladder was visualized by ultrasound.

A categorical diagnosis of gallstones was made by cholecystosonography in 26 of the above 42 or 62% of the cases with gallstones. There was not a false positive diagnosis of cholecystolithiasis. Diagnostic accuracy was 50% among 22 cases with gallstones studied prior to May of 1977 and 75% among 20 cases with gallstones studied since that time. These results are summarized in Table 2.

Despite a variety of attempts, the gallbladder was not visualized at any time by any cholangiographic technique in 26 of these 86 cases. Stones were proven to be present in 18 of these 26 cases. Cholecystosonography documented the presence of the stones in 12 of the 18 cases.

The response of the gallbladder to stimulation was observed in 24 cases, nine cases after a fatty meal and 15 cases after administration of cholecystokinin. A reduction in size of the gallbladder established a patent cystic duct in 18 of these 24 cases. Seventeen of these latter 18 cases were in the process of evaluation of an acute RUQ syndrome and one case with chronic RUQ pain was under study because of nonvisualization of the gallbladder by oral cholecystography.

The gallbladder did not reduce in size in six cases. A diagnosis of cholecystolithiasis was established in four of these six cases. The gallbladder and biliary tract were ultimately proven to be normal in the other two of these six cases, one case with pelvic inflammatory disease and one with urinary tract infection. These facts are summarized in Table 3.

Acute RUQ Syndrome

In each of these 53 cases the diagnosis of attempted gallstone migration and acute obstructive cholecystopathy was suspected. The serum bilirubin exceeded 1.5 mg % but was less than 3.0 mg % in 14 of the 53 cases. A diagnosis of cholecystolithiasis was ultimately established in 21 of these 53 cases. In all 21 of these cases attempted stone migration was determined to be the cause of the RUQ syndrome. The diagnosis of cholecystolithiasis was made correctly by cholecystosonography during the acute phase of the illness in 12 of the 21 cases or 57% of instances.

Oral cholecystography was attempted during the acute phase illness in nine and intravenous cholangiography in four others of the 21 cases with proven gallstones. In only one of these 13 instances of cholangiography was the gallbladder visualized. This was a case in which the gallbladder was visualized by intravenous cholangiography and a diagnosis of cholecystolithiasis was made. In contrast, a diagnosis of cholecystolithiasis was made by ultrasound in eight of these 13 cases which underwent cholangiography.

Among the 32 cases of acute RUQ syndrome in which cholecystolithiasis was ultimately proven not to be present, there were 15 cases in which the gallbladder was not stimulated during the cholecystosonographic examination. These 15 cases are excluded from further discussion. In 17 other cases of acute RUQ syndrome in which gallstones were ultimately proven not to be present, the gallbladder was stimulated during the sonographic study. This was achieved by a fatty meal in nine cases and by cholecystokinin in eight cases. In 16 of the 17 cases the gallbladder decreased in size. This event established patency of the cystic duct and was interpreted to exclude a diagnosis of acute obstructive cholecystopathy as a cause of the acute RUQ syndrome. In one case with pelvic inflammatory disease and a final diagnosis of venereal perihepatitis or Curtis-Fitzhugh Syndrome, the gallbladder did not reduce in size following administration of cholecystokinin. A subsequent oral cholecystogram visualized an apparently normal gallbladder without demonstrable gallstones.

A case in which documentation of reduction in size of the gallbladder following administration of cholecystokinin excluded a diagnosis of obstructive cholecystopathy was depicted as Figure 3.

Table 3. *Cholecystosonography: Gallbladder Stimulation**

	# Cases		
• Cases Studied			24
• Contraction		18	
Patent Cystic Duct	18		
• Noncontraction		6	
Patent Cystic Duct	2		
Cholecystolithiasis	4		

* Fatty meal—9, Cholecystokinin—15.

Cholestasis and Hepatic Dysfunction—11 Cases

The level of serum bilirubin exceeded 2.0 mg % or the serum glutamic oxalic transaminase 450 units in each of these cases. The degree of cholestasis or hepatic cellular dysfunction in each instance was such that hepatic excretion of dye might be compromised and preclude satisfactory visualization of the biliary ductal system by oral or intravenous cholangiography. The presence of gallstones was suspected in each case.

Gallstones were proven to be present in six of these 11 cases. A hepatocellular cause for cholestasis existed in the remaining five cases. The cholecystosonographic examination established the diagnosis of gallstones in four of the six cases with cholecystolithiasis.

Nonvisualization by Oral Cholecystography—10 Cases

In ten cases the gallbladder had not been visualized by oral cholecystography performed prior to cholecystosonography. In two of these ten cases a one day study had been performed after an ingestion of six tablets of iopanoic acid.* In the remaining eight cases a two day study had been performed with ingestion of six tablets on two consecutive nights. Concern did not exist regarding ingestion of dye, absorbtion of dye or any hepatic disease which might interfere with excretion of dye. Gallstones were present in eight of these ten cases and were documented by cholecystosonography in five of these eight cases.

The two remaining cases with nonvisualization of the gallbladder on oral cholecystosonography did not have final proof of stone disease of the biliary tract. In one of these two latter cases an intravenous cholangiogram was performed after the gallbladder was not visualized on a one day study. This revealed a dilated common bile duct which was confirmed by ultrasound. Total serum bilirubin was 0.95 mg %. At the time of the ultrasound examination a mass was seen in the region of the pancreatic head. The final pathological diagnosis was pancreatic cancer.

The final case of nonvisualization of the gallbladder by oral cholecystography was one of right upper quadrant abdominal pain in which the gallbladder had not been visualized on a presumably satisfactory two day study. Cholecystectomy was scheduled but a cholecystosonogaphic examination was performed preoperatively in an attempt to confirm the presumptive diagnosis of cholecystolithiasis. The gallbladder was identified, gallstones were not seen and the gallbladder reduced in size following administration of cholecystokinin. A repeat oral cholecystogram revealed an apparently normal gallbladder, without stones. Surgery was not performed.

Visualization of the Gallbladder by Cholecystosonography—11 Cases

Cholecystosonography was performed in 11 cases in which the biliary tract was visualized by cholecystography in an immediate adjacent period of time. The gallbladder was identified by ultrasound in ten of the 11 cases.

Gallstones were not present in five of these 11 cases. These cases will not be the basis for further discussion. In five of the remaining six cases, each with final proof of gallstones, the stones were documented by cholangiography in five and by ultrasound in three of these five. The sixth and final case is one in which a technically satisfactory oral cholecystogram did not reveal cholecystolithiasis. Cholecystosonography was reported as a categorical diagnosis of cholecystolithiasis which was confirmed at surgery. The density of the stone was the same as that of the contrast media and had resulted in a false negative oral cholangiogram. The cholangiographic and cholecystosonographic examinations of this patient are depicted in Figure 4.

Allergy to Contrast Media—1 Case

In one case with attacks characteristic of attempted gallstones migration, a documented history of anaphylactic reaction to iodine containing radiographic contrast media was obtained. Cholecystosonogaphy established the diagnosis of cholecystolithiasis. Facts concerning identification of cholecystolithiasis in each category of cases that were studied are summarized in Table 4.

Discussion

The demonstration in 1924 by Evarts Graham and Warren Cole of the Department of Surgery at Washington University that the gallbladder can concentrate radiopaque media and be radiologically visualized was a signal event.[12] Subsequent developments in imaging of the gallbladder stem from their report. Ultrasound is a new technique capable of imaging the gallbladder and gallstones.[9] A noninvasive procedure, it is performed without ionizing radiation. Pulsed ultrasound as currently employed for diagnostic purposes has not been shown to have any deleterious biological effects.[1] The accuracy of the new modality of cholecystosonography is being defined.[2,3,9,15,16]

---

* Telopaque, Winthrop Laboratories, New York, New York.

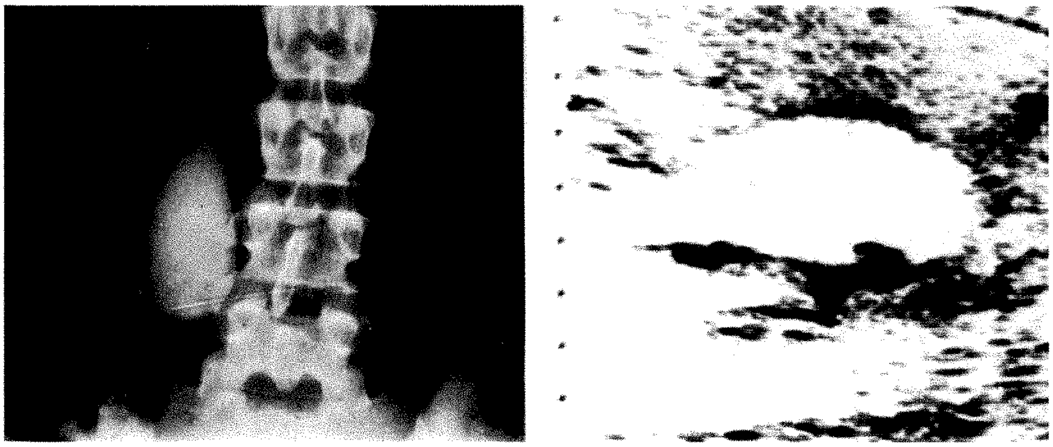


FIG. 4. An oral cholecystogram (left) in which the gallbladder is well visualized and stones are not seen. A cholecystosonogram in this case (right) was diagnostic of cholecystolithiasis.

The gallbladder was identified by ultrasound in 84 of the 86 cases of the present series. Absence of air in the stomach and duodenum and a full gallbladder consequent to the fasting state will enhance visualization. Obesity or contraction of the gallbladder will reduce ability to identify the gallbladder. The experience and persistence of the examiner is important. At the University of South Alabama all examinations are performed under direct physician supervision and the usual examination takes an average of 20 minutes, exclusive of any study of stimulation of the gallbladder.

The presence or absence of gallstones was established at surgery or by cholangiographic visualization of the gallbladder in all 86 cases in this report. Gallstones were proven to be present by cholecystosonography in 26 or 64% of 42 cases with proven gallstones. Stones less than 3 mm in diameter or in the cystic duct may be difficult to identify. Application of strict diagnostic criteria has thus far eliminated a false positive diagnosis.[17] The rate of diagnosis of gallstones has increased as experience has been gained. The maximal rate that can be achieved has yet to be determined.

Liberalization of criteria and use of indirect evidence would increase the rate of diagnosis of gallstones.

TABLE 4. *Cholecystosonography: Cholecystolithiasis*

Indications	No. Cases	Gallbladder Identified	Gallstones Present	Sonographic Dx. Calculi
RUQ Syndrome	53	53	21	12
Cholestasis	11	10	6	4
Confirm Oral Cholangiogram				
Nonvisualization	10	10	8	5
Visualization	11	10	6	4
Allergy to Contrast Media	1	1	1	1
	86	84	42	26

Among indirect criteria that could be considered for the diagnosis of cholecystolithiasis would be "distention" of the gallbladder. Attempts have been made to establish norms for the size and volume of the gallbladder.[9,19] The size of the normal gallbladder is highly variable. Other indirect diagnostic considerations would include "shadowing" without direct identification of the gallbladder and stones,[7] wall irregularity, stones imaged in only one projection without "shadowing" or failure of the gallbladder to distend in the fasting state to a diameter sufficient for visualization. This latter observation would be presumed to be due to chronic disease and a nondistensable gallbladder. The precise significance of these indirect criteria has not been established. Their application is likely to result in an increased number of false positive diagnoses. As experience is gained with cholecystosonography the reliability of indirect signs of cholecystolithiasis should become apparent.

During cholecystosonography the pancreas, liver, portahepatis and surrounding structures are observed. A mass in the pancreas or dilatation of the common duct may be noted and be diagnostically relevant. Indeed, the presence or absence of biliary ductal dilatation is central to the ultrasonic evaluation of the jaundiced patient.[8,14,20] Choledocholithiasis may be observed. Demonstration of gallstones in the distal common bile duct by ultrasound is more difficult than their demonstration in the gallbladder.

A comparison of diagnostic accuracy in one study to that in other studies is hazardous. Variation in patient selection, diagnostic criteria, and methods or reporting of results preclude easy comparisons. For example, Arnon and Rosenquist reported a 90% accuracy in 123 cases of cholecystosonography. Their report involved 39 cases with gallstones, of whom 30 were identified sonographically.[2] The report of Leopold and associates of 91% accuracy also includes a number of cases without gallstones.[16] In the final analysis, usefulness and credibility of the study is much more importantly related to a negligible incidence of false positive than a moderate incidence of false negative diagnoses. If the physician understands the limitations of this simple and noninvasive study, he can properly interpret a negative study and initiate other diagnostic procedures.

The patency of the cystic duct can be established during cholecystosonography by observation of reduction of size of the gallbladder following stimulation by a fatty meal or cholecystokinin.[10] With extraordinarily rare exception obstruction of the cystic duct is caused by gallstones. Thus, for practical purposes, reduction in size of the gallbladder following stimulation can exclude a diagnosis of obstructive cholecystopathy due to cholecystolithiasis. The converse is not true. Two cases were observed in which the biliary tract was apparently normal and the gallbladder did not reduce in size in response to stimulation by cholecystokinin.

The indications for cholecystosonography must be established as an alternative to, in preference to or subsequent to cholangiography by existing oral, intravenous, transhepatic and endoscopic retrograde methods.[4,13,18] The likelihood or actuality of visualization or nonvisualization of the gallbladder by the above methods and the risks of various types of cholangiography will be considerations in a decision to obtain a cholecystosonogram. Thus, a brief review of the current status of cholangiography is relevant to a consideration of indications for cholecystosonography.

Oral cholecystography is simple, safe and economical. In the elective situation it has been and remains the standard technique for evaluation of the gallbladder. When oral cholecystography results in visualization of the gallbladder, accuracy in the diagnosis of cholecystolithiasis is "98%." On rare occasion the gallstones may be of the same density as the contrast media and a false negative examination results.[6]

Nonvisualization of the gallbladder by oral cholangiography may be due to failure of ingestion, impaired intestinal absorption, failure of hepatic excretion or lack of concentration of the dye in the gallbladder.[5] Ileus due to an acute abdomen or mechanical enteric obstruction from any cause may interfere with absorption of the dye. Hepatic dysfunction or direct hyperbilirubinemia may preclude hepatic excretion of the dye. Iopanoic acid is excreted by the same pathway as bilirubin. Assuming ingestion, intestinal absorption and hepatic excretion of the dye, nonvisualization of the gallbladder by oral cholangiogram in over 90% of instances is due to a diseased gallbladder. Under these circumstances nonvisualization is considered a positive rather than a negative observation, but the diagnosis is still inferential. Almost always the disease in the gallbladder is either an obstructed cystic duct due to cholecystolithiasis or a chronically diseased gallbladder with cholecystolithiasis.

Problems associated with ingestion and absorption of dye can be avoided by intravenous cholangiography.[13] If hepatic function is adequate and hyperbilirubinemia is absent, the common bile duct will be visualized by intravenous cholangiography in over 90% of cases. The gallbladder is visualized following passive diffusion of dye into the gallbladder. In a small number of cases opacification may not be adequate for detection of gallstones. A normal gallbladder should be visualized by intravenous cholangiography in at least 85% of cases in which the common duct is visualized. When a diagnosis of acute obstructive cholecystopathy is suspected, intravenous cholangiography may exclude the diagnosis by demonstration of a visualized gallbladder. Conversely, nonvisualization may support a diagnosis of cystic duct obstruction. Serious drug reaction may occur during intravenous cholangiography.

Either percutaneous transhepatic or endoscopic retrograde cholangiography will obviate problems of ingestion, absorption and hepatic excretion of dye. Both are invasive procedures with definite, although low risk.

The above considerations regarding the various methods of cholangiography and the experience reported in this paper have provided the basis for our current policy for use of cholecystosonography when a diagnosis of cholecystolithiasis is suspected. Cholecystosonography has become the preferable first diagnostic study in cases of acute RUQ syndrome. Problems of ingestion, absorption and excretion of dye are eliminated. Gallstones may be demonstrated and, if not, administration of cholecystokinin may result in reduction in size of the gallbladder and exclude a diagnosis of acute obstructive cholecystopathy. A decision will be required regarding the clinical significance of demonstrable gallstones—the presence of stones does not establish their role in pathogenesis of the existing clinical disorder. If gallstones are not seen, other diagnostic procedures such as intravenous cholangiography can be initiated.

Prior to the advent of cholecystosonography, intravenous cholangiography was widely employed at the University of South Alabama Medical Center in evaluation of cases of acute RUQ syndrome. In the absence of prior diagnosis of cholecystolithiasis, and when feasible, an intravenous cholangiogram was performed before institution of treatment based on a diagnosis of acute obstructive cholecystopathy. At best, the result was an inferential diagnosis of gallstones consequent to a nonvisualized gallbladder rather than the positive diagnosis that may be established by cholecystosonography.

When cholestasis and hepatic dysfunction may preclude a valid oral or intravenous cholangiography, cholecystosonography is performed before proceeding to more complicated and invasive procedures such as percutaneous transhepatic cholangiography or endoscopic retrograde cholangio-pancreatography. The role of cholecystosonography as the first diagnostic study in the case of allergy to contrast media is obvious.

Experience reported in this paper supports the use of cholecystosonography as the first study for the diagnosis of cholecystolithiasis in the foregoing circumstances of acute RUQ syndrome, cholestasis and allergy to contrast media. It precedes any form of choangiography. This presupposes availability of the study and a professional staff with keen interest in this diagnostic modality.

The role of cholecystosonography in confirmation of the result of presumably valid elective oral cholangiography requires definition.[3] Occasionally the gallbladder is visualized, stones are not seen but, consequent to a typical history, the diagnosis of cholecystolithiasis is still suspected. Gallstones may be present of the same density as the contrast media—a rare false negative examination.[6] Cholecystosonography may detect such gallstones. A role for cholecystosonography in the case in which there is not reason to question dye ingestion, absorption or excretion and in which the gallbladder is not visualized by cholangiography is less clear. In this situation an inferential diagnosis of cholecystolithiasis is greater than 90% accurate, exceeding the present accuracy of cholecystosonography. A pilot study has been initiated at the University of South Alabama Medical Center in these cases. Prior to surgery with a diagnosis of chronic cholecystitis with cholecystolithiasis based on cholangiographic nonvisualization of the gallbladder, cholecystosonography is performed. The question under study is whether cholecystosonography can, under these circumstances, be complimentary to oral cholangiography.

References

1. American Institute of Ultrasound in Medicine: Bio-Effects Committee, August 1976. Reflections, 3(1):18, 1977.
2. Arnon, S. and Rosenquist, C. J.: Gray Scale Cholecystosonography: An Evaluation of Accuracy. Am. J. Roentgenol. 127:817, 1976.
3. Bartrum, R. J., Jr., Crow, H. C. and Foote, S. R.: Ultrasonic and Radiographic Cholecystography. N. Engl. J. Med., 296:538, 1977.
4. Baker, H. L., Jr. and Hodgson, J. R.: Further Studies on the Accuracy of Oral Cholecystography. Radiology, 74:239, 1960.
5. Berk, R. N., Loeb, P. M., Goldberg, L. E., Sokoloff, J.: Medical Progress: Oral Cholecystography with Iopanoic Acid. N. Engl. J. Med., 290:204, 1974.
6. Cole, W. H.: The False-Normal Oral Cholecystogram. Surgery, 81:121, 1977.
7. Crow, H. C., Bartrum, R. M., Jr. and Foote, S. R.: Expanded Criteria for the Ultrasonic Diagnosis of Gallstones. J. Clin. Ultrasound, 4:289, 1976.
8. Goldberg, B.: Ultrasonic Cholangiography. Radiology, 118: 401, 1976.
9. Goldberg, B. B., Harris, K. and Broocker, W.: Ultrasonic and Radiographic Cholecystography. Radiology, 111:405, 1974.
10. Goldberg, H. I.: Cholecystokinin Cholecystography. Semin. Roentgenal., 11:175, 1976.
11. Goldstein, L. I., Sample, W. F., Kadell, B. M., Weiner, M.: Gray-Scale Ultrasonography and Thin-Needle Cholangiography. JAMA, 238:1041, 1977.
12. Graham, E. A. and Cole, W. H.: Roentgenologic Examination of the Gallbladder: New Method Utilizing Intravenous Injection of Tetrabromphenolphthalein. JAMA, 82:613, 1924.
13. Hatfield, P. M. and Wise, R. E.: Radiology of the Gallbladder and Bile Ducts. Baltimore, Williams & Wilkins, 1976.
14. Isikoff, M. B. and Diaconis, J. N.: Ultrasound: A New Diagnostic Approach to the Jaundiced Patient. JAMA, 238:221, 1977.
15. Lawson, T. L.: Grey Scale Cholecystosonography. Radiology, 122:247, 1977.
16. Leopold, G. R., Amberg, J., Gosink, B. B., Mittelstaedt, G. R.: Grey Scale Ultrasonic Cholecystography: A Comparison With Conventional Radiographic Techniques. Radiology, 121: 445, 1976.
17. McCune, B. R., Weeks, L. E., O'Brien, T. F., Jr. and Martin, J. F.: "Pseudostone" of the Gallbladder—Ultrasound Findings and Case Report. Gastroenterology, 73:1149, 1977.
18. Ochsner, S. F.: Performance and Reliability of Cholecystography. South. Med. J., 63:1268, 1970.
19. Redman, H. C. and Reuter, S. R.: The Angiographic Evaluation of Gallbladder Dilatation. Radiology, 97:367, 1970.
20. Vicary, F. R., Cusick, G., Shirley, I. M. and Blackwell, R. J.: Ultrasound and Jaundice. Gut, 18:161, 1977.

DISCUSSION

DR. ROBERT S. SPARKMAN (Dallas, Texas): (Slide) The subject that Dr. Donovan and his associates have presented so ably is one that is of great interest to us at Baylor Medical Center in Dallas. Our experience with ultrasound in abdominal diagnosis began four years ago, in 1973. The number of these examinations that we are performing now approaches 5000 per year, and of this number 600–900 are specifically for the investigation of the gallbladder and the bile ducts.

We agree that ultrasound should be used first in patients with jaundice, vomiting, allergy to iodine, and in emergency situations. However, it is also the procedure of choice in gallbladder diagnosis in pregnancy, since the fetus is not subjected to any risk of genetic damage from irradiation. Our experience with about 50 such cases has been very gratifying.

(Slide) This shows a distended urinary bladder, and beneath it the gravid uterus, and in the same patient gallstones are demonstrated.

We do not believe that sonography is the procedure of choice for routine diagnostic study of the gallbladder. We have been especially interested in attempting to define the limitations of this procedure.

(Slide) This demonstrates the interference of gas shadows, and we find that the colon is a much greater source of trouble than the stomach and duodenum.

(Slide) A very small, contracted gallbladder, such as this one, or a solid gallbladder may be impossible to (slide) demonstrate by ultrasound.

(Slide) The technical factors limiting cholecystosonography in our experience are gas, obesity, a tiny or solid gallbladder, scattered small stones, a high position of the gallbladder, and, rarely, the inability of the patient to cooperate.

But perhaps of even greater importance (slide) are the limitations that are correctable, and these include availability of the examiner, the experience of the examiner, and his persistence. And as these factors are corrected, the incidence of correct diagnosis will increase.

(Slide) For example, this patient was allergic to iodine, (slide) and two sonograms, including this one, failed to demonstrate stones. But a third examination (slide) demonstrated stones quite clearly, which shows the value of persistence in this examination. (Slide) And the cholecystographic report was: "Unequivocal gallstones," which is the kind of report that you like to receive. (Slide) And these are the gallstones that were recovered from that patient.

Finally, we have not used the cholecystokinin or fatty meal studies in any of our patients, but perhaps this would give us additional information that might be valuable to us.

Dr. James D. Hardy (Jackson, Mississippi): I first learned of these data when I visited Dr. Donovan at Mobile, where his outstanding leadership with his new department at the University of South Alabama is apparent on all sides.

Our experience has been very similar to that presented by the essayist and by Dr. Sparkman with his remarkable slides. In general, sonography has been most useful when the gallbladder failed to visualize on cholecystogram; or rarely where it did visualize, where stones were suspected, but where stones could not be seen, because of almost identical opacity of stones and media.

I will not repeat the points which Dr. Sparkman has made so well. I will simply close by asking Dr. Donovan if he cares to compare the accuracy of sonography with the much more expensive CT scanning.

Dr. Gardner, W. Smith (Baltimore, Maryland): He has already enumerated the situations in which sonographic visualizations of the gallbladder may be especially indicated, and in general we would agree. We have evaluated this technique in the diagnosis of gallbladder disease in 103 patients, and I just want to summarize that on one slide.

(Slide) In 50 of these patients gallstones were visualized, and in 46 of them the gallbladder was interpreted as normal. There were seven nonvisualized studies, and I think it's important to point out that nonvisualization on a sonogram of the gallbladder is meaningless. It refers, as Dr. Sparkman indicated, to a technical problem of some kind; but it doesn't mean the same thing as nonvisualization is said to mean on an oral cholecystogram.

We did, however, have three false positive studies, and two false negative ones. If you count these plus the seven studies that were failures, the overall gross accuracy of the technique in our experience was 88%.

We had hoped that sonography would be especially useful in confirming the presence of gallstones when the gallbladder fails to visualize on a sequential dose oral cholecystogram. We had 53 such patients, (slide) and the next slide outlines what we, in fact, learned from that. Unfortunately, only nine patients were proven to have stones on sonography with nonvisualizing oral cholecystograms; and furthermore, there was one false positive. Only four patients were demonstrated to have normal gallbladders with nonvisualizing oral cholecystograms, and there were two false negatives.

It would have been especially nice if the sonogram had proven that these 23 patients with nonvisualization of the gallbladder on sequential dose oral cholecystography had normal gallbladder; but, in fact, as you can see, we didn't succeed in doing this, and I'm afraid that our study is inconclusive in determining the value of sonography with nonvisualization on the oral cholecystogram.

(Slide) Only 34 of our patients had their sonographic studies confirmed by operation, but these confirmed results do suggest the reliability of the technique. (Slide) As you can see, the sonography has a sensitivity of 86% in the detection of stones, and a specificity of 78% in showing no stones, giving an overall accuracy of 84% in this experience. And by contrast it's interesting that the cholecystography in these patients had an overall accuracy of only 73%. There's no statistical difference, but it is interesting.

There is one caution which we learned, however. As a result of this kind of experience, everybody got a little enthusiastic about sonograms, and they began to be used as a screening technique for the diagnosis of gallstones. I think that in these days of cost-consciousness this is not an appropriate way to use the procedure. And my next and last slide shows you why.

(Slide) At least in our institution, the sonogram costs $23 more than an oral cholecystogram, even when the latter has to be repeated; it's hard to justify doing that as the initial screening technique.

I would also agree with Dr. Sparkman that there is one other indication for this procedure which we would add to the ones that Dr. Donovan mentioned: the pregnant patient.

Dr. Frank Glenn (New York, New York): You have heard two papers this morning that emphasize something very fundamental, and that is: Improvement in therapy is often, and usually, dependent on accurate diagnosis. And Dr. Sabiston's paper certainly was a good lead-off, and this is in the same vein.

We have been interested in this subject for some time. The discussants have covered the subject well, and I think the essayists have done a superb job.

We have been particularly interested in the differential diagnosis of jaundice, something that has bothered every surgeon, I'm sure, just like it's bothered me, that is parenchymal disease, obstructive jaundice. We have now accumulated some 60 odd cases in which this was the primary problem.

And our accuracy of diagnosis, as estimated not only by the surgeons, but also by the head of our Roentgenology Department, is around 92%. This is a great advance.

The safety of the procedure is, of course, evident.

I would add on to the comments of the previous discussion that in sonography for differential diagnosis between parenchymal and obstructive jaundice one should bear in mind the possibility of mistaking a dilated or an enlarged portal vein for an obstructive duct. It is also important to evaluate the pancreas. Tumors of the pancreas can be visualized well by sonography and are often of course the cause of obstruction of the common duct. In children and infants sonography provides a method of demonstrating congenital cystic duct dilatations. In all instances not only are AP and lateral views indicated but also sagittal sections. From a standpoint of the gallbladder, cholecystokinin administration enables one to evaluate the function of the gallbladder and in some instances will dislodge stones so that they become evident.

I believe that the use of sonography will be of great value in experimental work. We have a model of a nonhuman primate we are using, essentially it consists of giving a baboon that has become pregnant, high cholesterol, high caloric diet so that she gains 20% of her body weight within the first trimester of pregnancy. This results in calculi formation and this method will enable us to observe when, in the course of pregnancy under these circumstances, stones first develop and to follow them with repeated observations to gain an idea of the rate of increase in size and number of the stones. This will be equally applicable to women who we believe to be likely to form gallstones during their pregnancy on the basis of family history. I need not emphasize to you the importance of investigative work upon the development of biliary calculi. This is a major health problem and comparatively speaking for the cost it imposes upon the people of this country a very small amount of money is being expended to obtain information that will enable us to reduce the incidence of the disease.

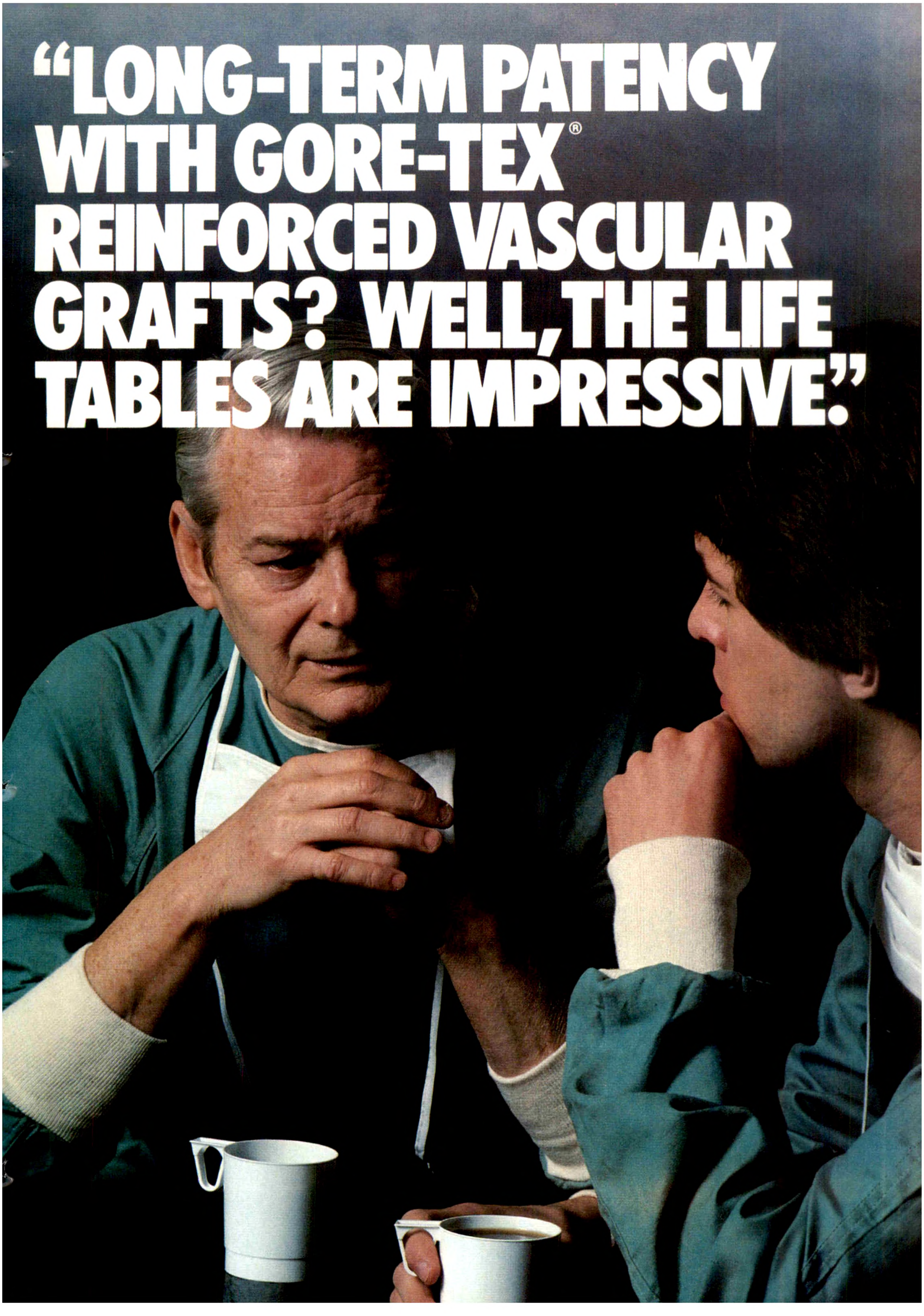
Dr. Arthur J. Donovan (Closing discussion): The point made by both Dr. Smith and Dr. Sparkman concerning pregnancy is, of course, a very valid point.

With respect to Dr. Hardy's question regarding cost, it is my understanding that the cost of the ultrasound is far less than that of the CT scan. I cannot give you any information based on personal experience on the relative accuracy of these two procedures. It is my understanding from discussion with radiologists that there are instances in which the gallbladder is visualized and stones are seen by ultrasound that are missed by the whole body scan, and, conversely, there have been instances in which the stones have been seen by the CT scan and missed by the ultrasound. The relative accuracy of these two procedures will have to be established.

Both Dr. Sparkman and Dr. Smith raised the question of the case of the nonvisualized gallbladder by cholangiography. Although I largely avoided that question this morning, it is considered in the manuscript. This is a very difficult matter concerning which we do not have enough accurate information to provide an answer. As an example, in a recent patient who had rather vague upper abdominal pain, the gallbladder was not visualized on a two day cholangiographic study, without reason to question the validity of the study. We now screen such patients by ultrasound preoperatively and performed cholecystosonography. There was not a stone seen in the gallbladder, which was visualized and which shriveled up following administration of cholecystokinin. We did not operate on this patient, but one may question whether we were right or wrong. Our accuracy in detection of gallstones by cholecystosonography is three out of four at the present time. Did we refuse surgery to a patient who was the one in four in whom we do not see the stones by sonography? Was the nonvisualization on the oral cholangiogram in a sense a false positive result? Only the experience that develops over the next few years will establish the role of cholecystosonography in relationship to the elective oral cholangiography, a diagnostic study with a superb record. Conversely, in the emergent situation, the jaundiced patient, the patient with allergy, or the pregnant patient the role of cholecystosonography is rather obvious.

Dr. Glenn commented with respect to the use of cholecystosonography in the differential diagnosis of jaundice. In the jaundiced patient the question of indirect signs, such as dilatation of the biliary ductal system in obstructive jaundice versus a small duct in the hepatocellular form of jaundice becomes central to the diagnosis. It is much more difficult to identify stones in the distal common duct than the gallbladder.

Finally, I would simply emphasize once more that the interest, the skill, and the persistence of the examiner is critical. All of our examinations are done by physicians. We have had an excellent record without false positive diagnoses. It's our position that we can accept a certain incidence of false negatives, but that a significant number of false positives would seriously jeopardize the usefulness of the study.


"LONG-TERM PATENCY WITH GORE-TEX® REINFORCED VASCULAR GRAFTS? WELL, THE LIFE TABLES ARE IMPRESSIVE."

LIFE TABLES CONFIRM HI
REINFORCED GRAFTS IN FE

s part of our continuing patency studies of e use of GORE-TEX reinforced vascular rafts (over 32,000 implants; 5,000 follow-ups) e have searched our data for all information om all surgeons reporting 25 or more rocedures with the use of GORE-TEX grafts in wer extremities, with follow-up periods of 12 onths or longer. The results — shown in ese pages — are gratifying.

THE PATIENT POPULATION.

There were 375 procedures performed on patient population that is, we think you'll gree, representative of the universe that most frequently requires cardio-vascular lower-extremity surgery, heavily skewed toward the older age groups. (89%, 51 years or over; with 70.1% showing symptoms of rest pain or necrosis; and 78.8% having 2 or fewer run-off vessels. (See Tables 1, 2, 3, below.)

THE RESULTS.

The life-table graphs shown here, especially Graph 1, tell the story better than words can. In Graph 1, we have included, for reference, the life-table analysis from the landmark Darling-Linton femoropopliteal Study using autogenous saphenous veins.[1]

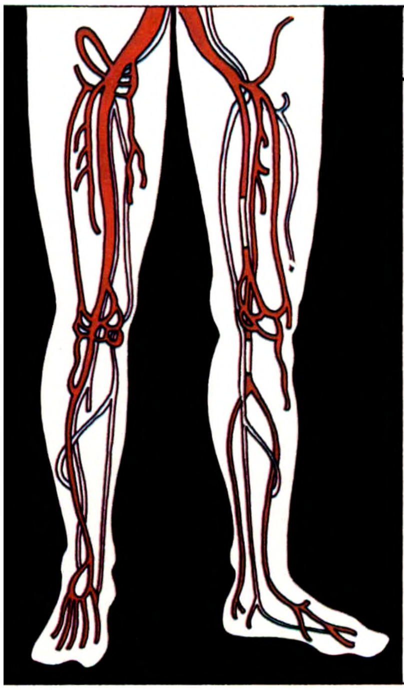
Table 1.	Population Symptoms[2]
Claudication	29.9%
Rest pain	34.0%
Necrosis	36.1%

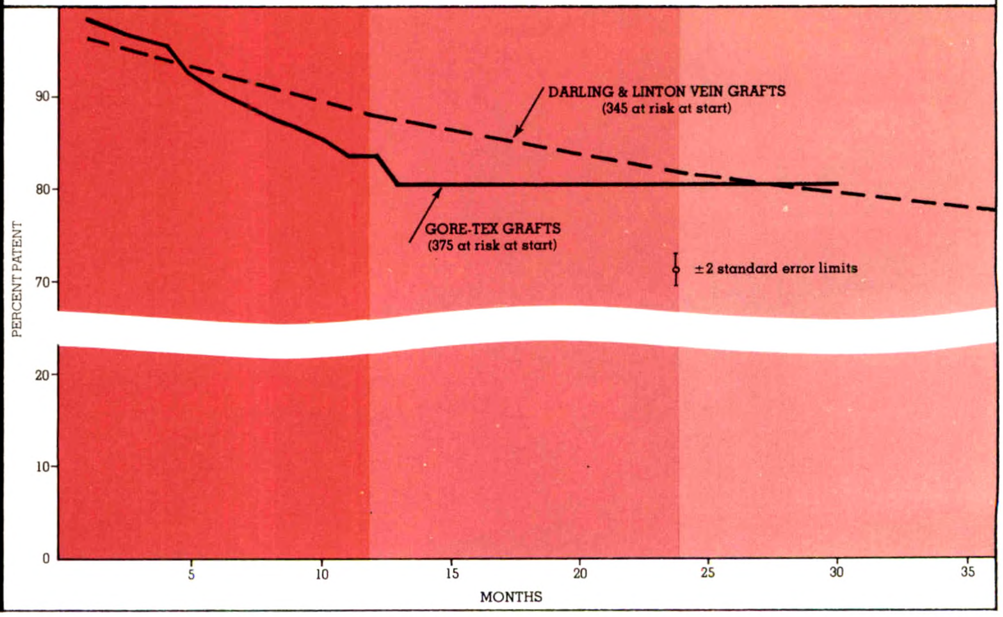
Table 2.	Population age[1]
21-30	0.4%
31-40	1.0%
41-50	9.6%
51-60	25.4%
61-70	31.6%
71-80	27.3%
81-90	4.3%
91-100	0.4%

[1] Based on full population

Table 3.	Available Run-off Vessels[2]
3 vessels	21.1%
2 vessels	43.8%
0-1 vessels	35.0%

[2] Patients for whom data on Symptoms or Run-Off Vessels were not reported were distributed in the same proportions as others for whom data were available.





Graph 1.: Life-table analysis, above and below knee femoral-popliteal. At risk: 375.

H PATENCY OF GORE-TEX®
OROPOPLITEAL BYPASSES.

As you can see, the line for GORE-TEX grafts holds within ± 2% of the Darling-Linton results through the first 31 months.

WHY GORE-TEX GRAFTS?

Many of the benefits of GORE-TEX vascular grafts arise directly from the nature of the material. It is expanded PTFE with a low-density, approximately 80% porous, structure.

The open structure of the GORE-TEX vascular graft allows tissue ingrowth, capillary formation, and perivascular adhesion, promoting the establishment of a thin, viable neointima.

Unlike Dacron*, there is no need to pre-clot.

ONE IMPORTANT IMPROVEMENT: INCREASED RESISTANCE TO ANEURYSMAL DILATATION.

Expanded PTFE has one drawback: low circumferential strength.

In early studies, this manifested itself primarily in the form of aneurysms, particularly in hypertensive patients.

Accordingly, in 1975, we reinforced GORE-TEX vascular grafts by winding a strong, fine lattice of expanded PTFE arounc the exterior.

This reinforcement imparts several important properties:

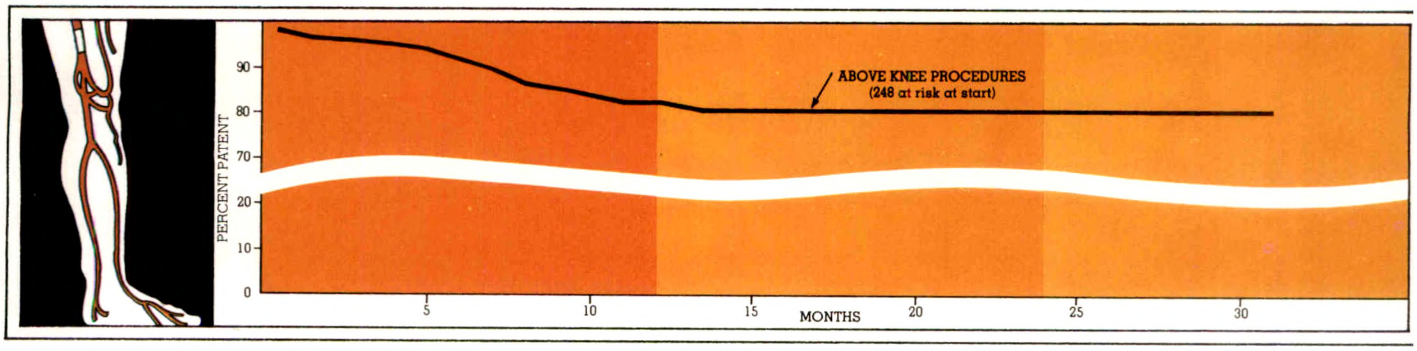
1. High radial or bursting strength, yielding outstanding resistance to dilatation. We test every GORE-TEX graft to 3600 mm H at 72°F, equivalent to approximately 70 p.s.i.
2. High suture holding power. (We invit you to test this for yourself in our offer on the last page of this advertisement.)

---

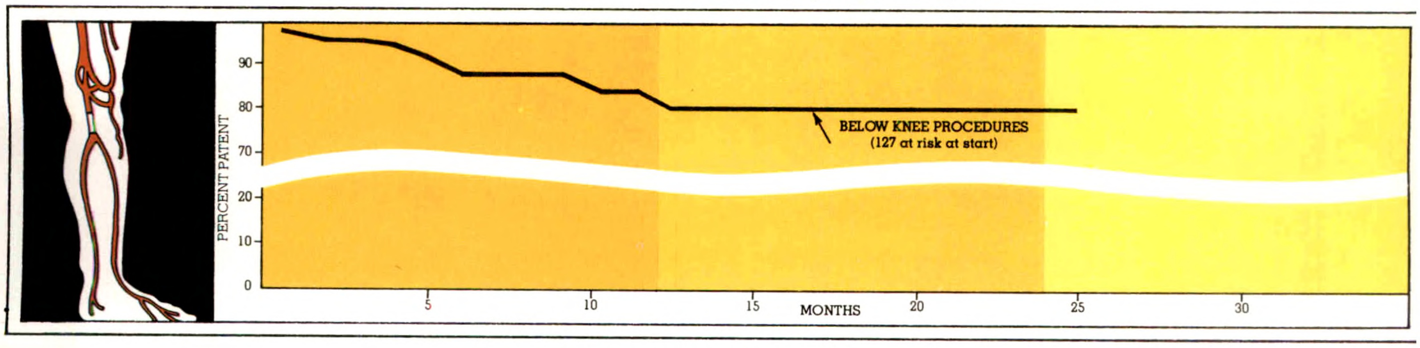
*Registered T.M. E.I. Du Pont
GORE-TEX is a registered T.M. of W.L. Gore.

[1] **Durability of Femoropopliteal Reconstructions;** Endartectomy versus Vein Bypass Grafts. R. Clement Darling, M.I Robert R. Linton, M.D. **American Journal of Surgery,** April, 1972. **Please note that the Darling-Linton patency rates were given fo ten years. In this report, we are comparing results for only 31 months.**

Graph 2.: Life-table analysis, above-knee femoral-popliteal. At risk: 248.

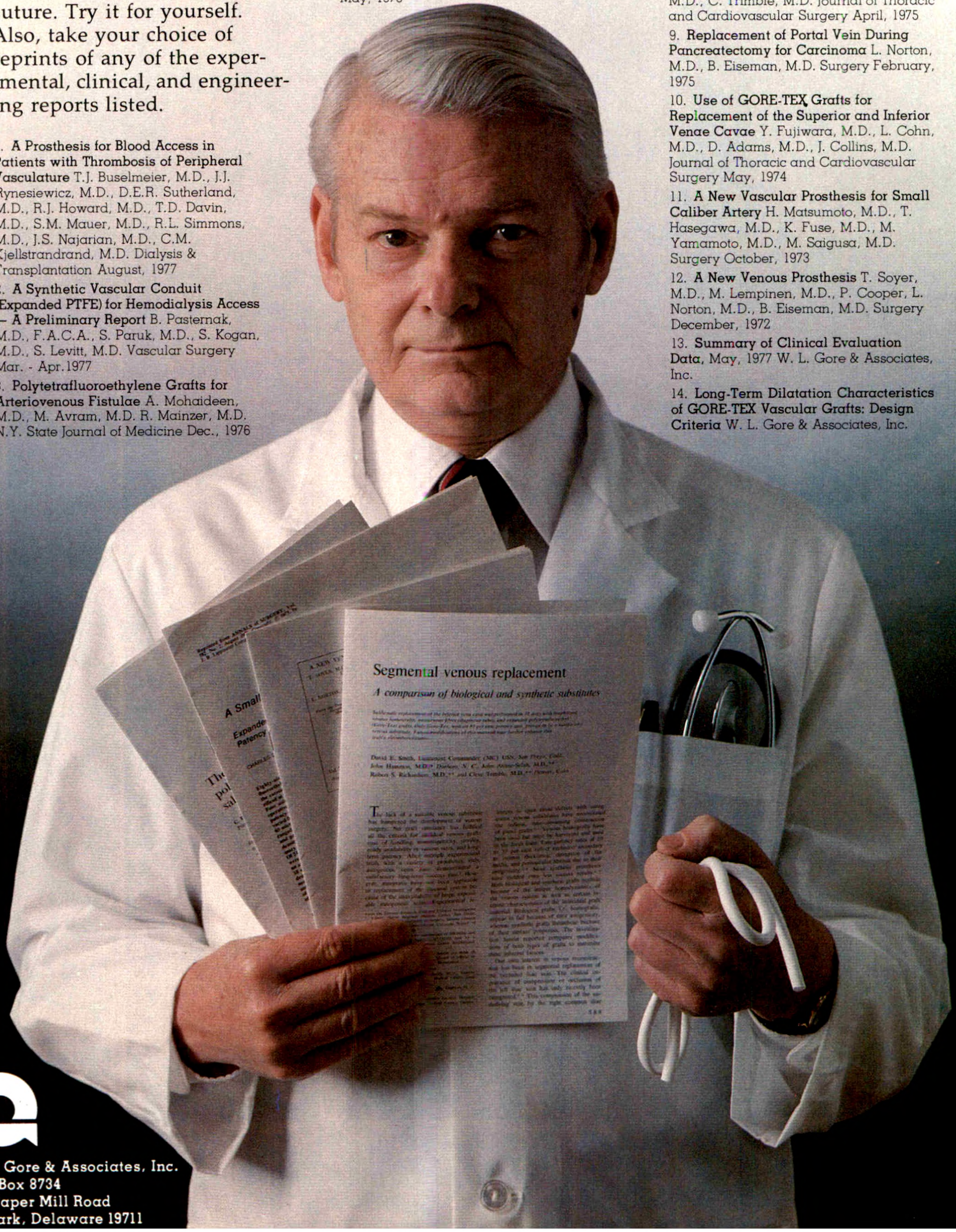


Graph 3.: Life-table analysis, below-knee femoral-popliteal. At risk: 127.



Submit the handling and suture-holding characteristics of GORE-TEX grafts to the most meaningful test equipment: your own hands. Our test kit, not intended for actual surgery, includes a short length of a GORE-TEX graft and a 6-0 double-armed suture. Try it for yourself. Also, take your choice of reprints of any of the experimental, clinical, and engineering reports listed.

1. **A Prosthesis for Blood Access in Patients with Thrombosis of Peripheral Vasculature** T.J. Buselmeier, M.D., J.J. Rynesiewicz, M.D., D.E.R. Sutherland, M.D., R.J. Howard, M.D., T.D. Davin, M.D., S.M. Mauer, M.D., R.L. Simmons, M.D., J.S. Najarian, M.D., C.M. Kjellstrandrand, M.D. Dialysis & Transplantation August, 1977
2. **A Synthetic Vascular Conduit (Expanded PTFE) for Hemodialysis Access — A Preliminary Report** B. Pasternak, M.D., F.A.C.A., S. Paruk, M.D., S. Kogan, M.D., S. Levitt, M.D. Vascular Surgery Mar. - Apr. 1977
3. **Polytetrafluoroethylene Grafts for Arteriovenous Fistulae** A. Mohaideen, M.D., M. Avram, M.D. R. Mainzer, M.D. N.Y. State Journal of Medicine Dec., 1976
4. **Arterial Prosthesis of Microporous Expanded Polytetrafluoroethylene for Construction of Aorta-Pulmonary Shunts** A. Gazzaniga, M.D., J. Lamberti, M.D., R. Siewers, M.D., D. Sperling, M.D., W. Dietrick, M.D., R. Arcilla, M.D., R. Replogle, M.D. Journal of Thoracic and Cardiovascular Surgery Sept., 1976
5. **The Use of Expanded Microporous Polytetrafluoroethylene For Limb Salvage: A Preliminary Report** C. Campbell, M.D., D. Brooks, M.D., M. Webster, M.D., H. Bahnson, M.D. Surgery May, 1976
6. **Small-vessel Replacement with GORE-TEX (Expanded Polytetrafluoroethylene)** A. Florian, M.D., L. Cohn, M.D., G. Dammin, M.D., J. Collins, M.D. Archives of Surgery, March, 1976
7. **A Small Arterial Substitute: Expanded Microporous Polytetrafluoroethylene: Patency versus Porosity** C. Campbell, M.D., D. Goldfarb, M.D., R. Roe, M.D. Annals of Surgery August, 1975
8. **Segmental Venous Replacement** D. Smith, Lt. Cmdr. (MC) USN, J. Hammon, M.D., J. Anane-Sefah, M.D.R. Richardson, M.D., C. Trimble, M.D. Journal of Thoracic and Cardiovascular Surgery April, 1975
9. **Replacement of Portal Vein During Pancreatectomy for Carcinoma** L. Norton, M.D., B. Eiseman, M.D. Surgery February, 1975
10. **Use of GORE-TEX Grafts for Replacement of the Superior and Inferior Venae Cavae** Y. Fujiwara, M.D., L. Cohn, M.D., D. Adams, M.D., J. Collins, M.D. Journal of Thoracic and Cardiovascular Surgery May, 1974
11. **A New Vascular Prosthesis for Small Caliber Artery** H. Matsumoto, M.D., T. Hasegawa, M.D., K. Fuse, M.D., M. Yamamoto, M.D., M. Saigusa, M.D. Surgery October, 1973
12. **A New Venous Prosthesis** T. Soyer, M.D., M. Lempinen, M.D., P. Cooper, L. Norton, M.D., B. Eiseman, M.D. Surgery December, 1972
13. **Summary of Clinical Evaluation Data,** May, 1977 W. L. Gore & Associates, Inc.
14. **Long-Term Dilatation Characteristics of GORE-TEX Vascular Grafts: Design Criteria** W. L. Gore & Associates, Inc.


Segmental venous replacement
A comparison of biological and synthetic substitutes
A Small
Expande
Patency

V. L. Gore & Associates, Inc.
.O. Box 8734
55 Paper Mill Road
ewark, Delaware 19711

GORE-TEX® REINFORCED VASCULAR GRAFTS

To sterilize

Grafts may be sterilized using steam, gas, or flash autoclave techniques. Follow instructions on package and equipment.

Indications

1. Use a 5-0 or 6-0 nonabsorbable monofilament suture with a cardiovascular needle for best results on graft diameters of 6mm. or less. Larger sutures may be used with larger diameter grafts.
2. Intra-operative inspection of anastomoses using irrigant solutions may result in serum leakage when blood flow is established in the graft. To prevent this, care must be taken not to generate syringe pressures sufficient to force irrigant through the graft walls. To do so will alter the hydrophobic (non-wetting) properties of the GORE-TEX graft. (See Contraindication #11.)
3. Trim grafts to desired lengths using sharp surgical scissors. Grafts should be handled with clean forceps or gloves. GORE-TEX grafts are not "elastic." Therefore, proper matching of lengths is essential. If the graft is cut too short, excessive stress may be placed on the sutures and graft at the anastomosis. (See Contraindication #10.)

Contraindications

1. Do not pre-clot the graft.
2. Do not sterilize by irradiation techniques.
3. Grafts should never be exposed to temperatures exceeding 482°F (250°C).
4. Do not sterilize more than three times.
5. During sterilization, do not place grafts under heavy or sharp objects which might crush the graft during the sterilization cycle.
6. Do not attempt to sterilize the label attached to the PVC blister tray at high temperatures, as the materials (ink and adhesives) on the label may contaminate objects in contact with the label during the sterilization cycle.
7. Do not handle graft with ungloved hands. It should be handled with clean instruments.
8. Do not attempt to resterilize any unused graft portion which has been contaminated with blood or any foreign material.
9. Do not use absorbable sutures.
10. Do not cut graft while holding under tension. Doing so may cause separation of the outer layer.

    The GORE-TEX graft is a composite structure consisting of an inner base tube and a thin outer layer which reinforces the base tube to prevent aneurysmal dilatation. Do not use any portion of a GORE-TEX graft which has damage to, or separation of, the outer layer of the graft. Should the outer reinforcing layer become frayed at the end of the graft, do not pull on or peel the outer layer from the base tube. Carefully trim off the portion of the graft where the outer layer is frayed.
11. Do not force irrigating solutions through the GORE-TEX graft. Doing so may result in serum leakage after blood flow is established.
12. Do not place grafts in any fluid prior to use. Doing so may result in serum leakage after blood flow is established.
13. Puncturing the graft with a needle of the type commonly used for blood access can result in mechanical damage to the graft, in spite of the reinforcement mentioned in Contraindication #10.

    When this graft is punctured, it is essential that the needle puncture sites be spaced along the accessible subcutaneous length of the graft. Repeated needle puncture of the graft at the same site, or within the same immediate area, may result in mechanical damage to the graft which could result in hematoma, false aneurysm, or true aneurysm. Patients should be carefully observed so that appropriate action can be taken if hematoma or aneurysm should occur.

W. L. Gore & Associates, Inc.
P.O. Box 8734
555 Paper Mill Road
Newark, Delaware 19711

Gentlemen:

☐ Please send me your GORE-TEX test kit.

☐ Please send me the reprints and reports whose number I have circled.

1. 2. 3. 4. 5. 6. 7.
8. 9. 10. 11. 12. 13. 14.

☐ Please have your representative call for an appointment.

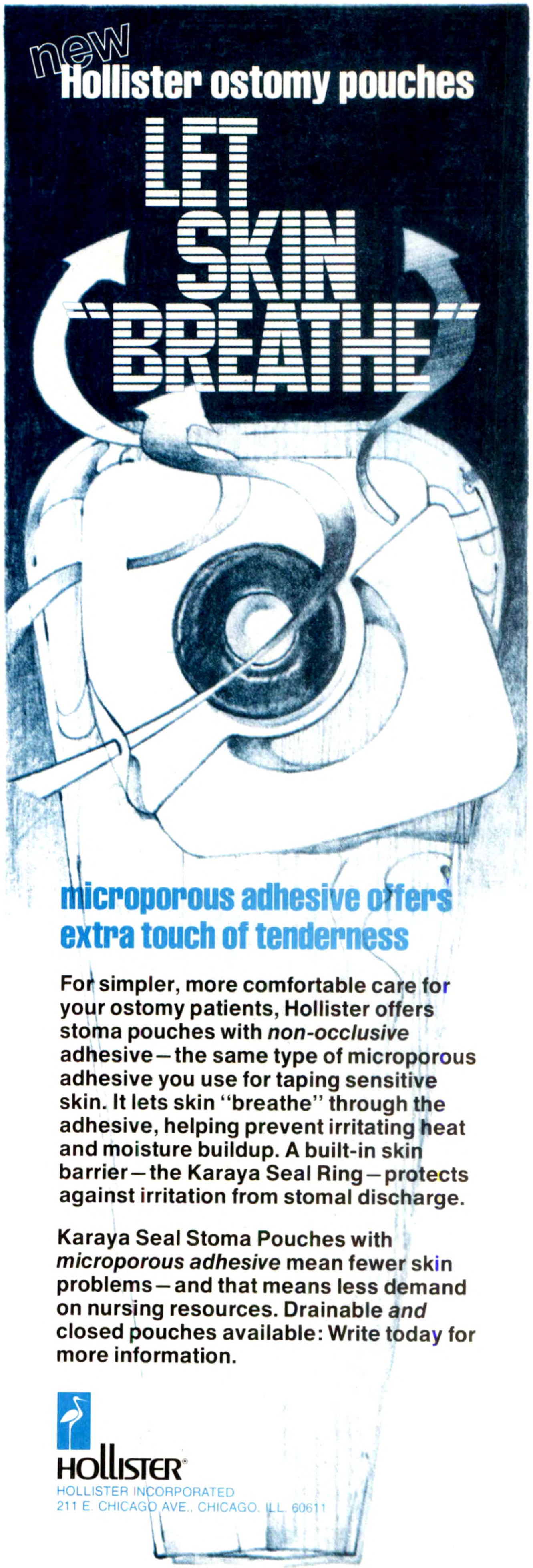
Name ____________________

Address ____________________

City ____________ State ____________ Zip ____________

Hospital Affiliation ____________________

Surgical Specialty ____________________

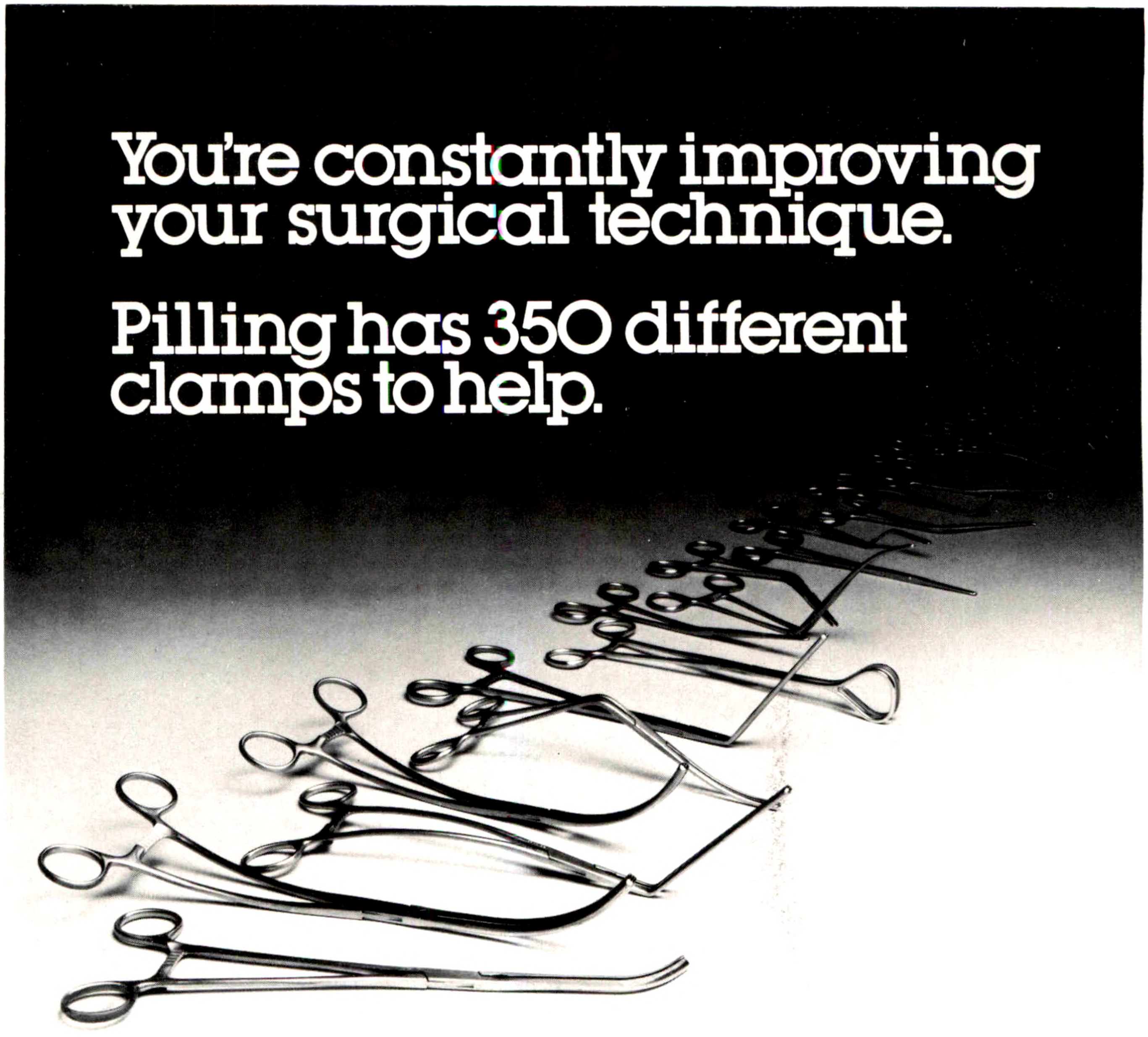


microporous adhesive offers extra touch of tenderness

For simpler, more comfortable care for your ostomy patients, Hollister offers stoma pouches with *non-occlusive* adhesive—the same type of microporous adhesive you use for taping sensitive skin. It lets skin "breathe" through the adhesive, helping prevent irritating heat and moisture buildup. A built-in skin barrier—the Karaya Seal Ring—protects against irritation from stomal discharge.

Karaya Seal Stoma Pouches with *microporous adhesive* mean fewer skin problems—and that means less demand on nursing resources. Drainable *and* closed pouches available: Write today for more information.

HOLLISTER®
HOLLISTER INCORPORATED
211 E. CHICAGO AVE., CHICAGO, ILL. 60611



You're constantly improving your surgical technique.

Pilling has 350 different clamps to help.

Pilling gives you the greatest available selection of vascular clamps — more than any other company — precisely matching the anatomical considerations for almost every surgical approach you use.

Regardless of the vessel to be occluded, you get complete vessel control efficiently and safely. Non-traumatic Atraugrip® jaw serrations — patented by Pilling and now widely imitated, grasp vessels firmly without crushing. You get complete vessel occlusion with intimal protection.

We've taken the most common point of breakage, the box lock, and developed a patented process that makes the box lock virtually indestructible. It will not break! Our Life-Lok® box lock construction protects your patient and assures confidence in your clamps.

We want to send you full specifications on the clamps that can enhance your surgical technique. Call us direct. We'll send you our 240 page catalog showing how Pilling clamps can do more for you in the operating room than any other clamps.

Call Toll Free Ask for Pilling's latest catalog of vascular, thoracic, and cardiac instruments.

800-523-6507

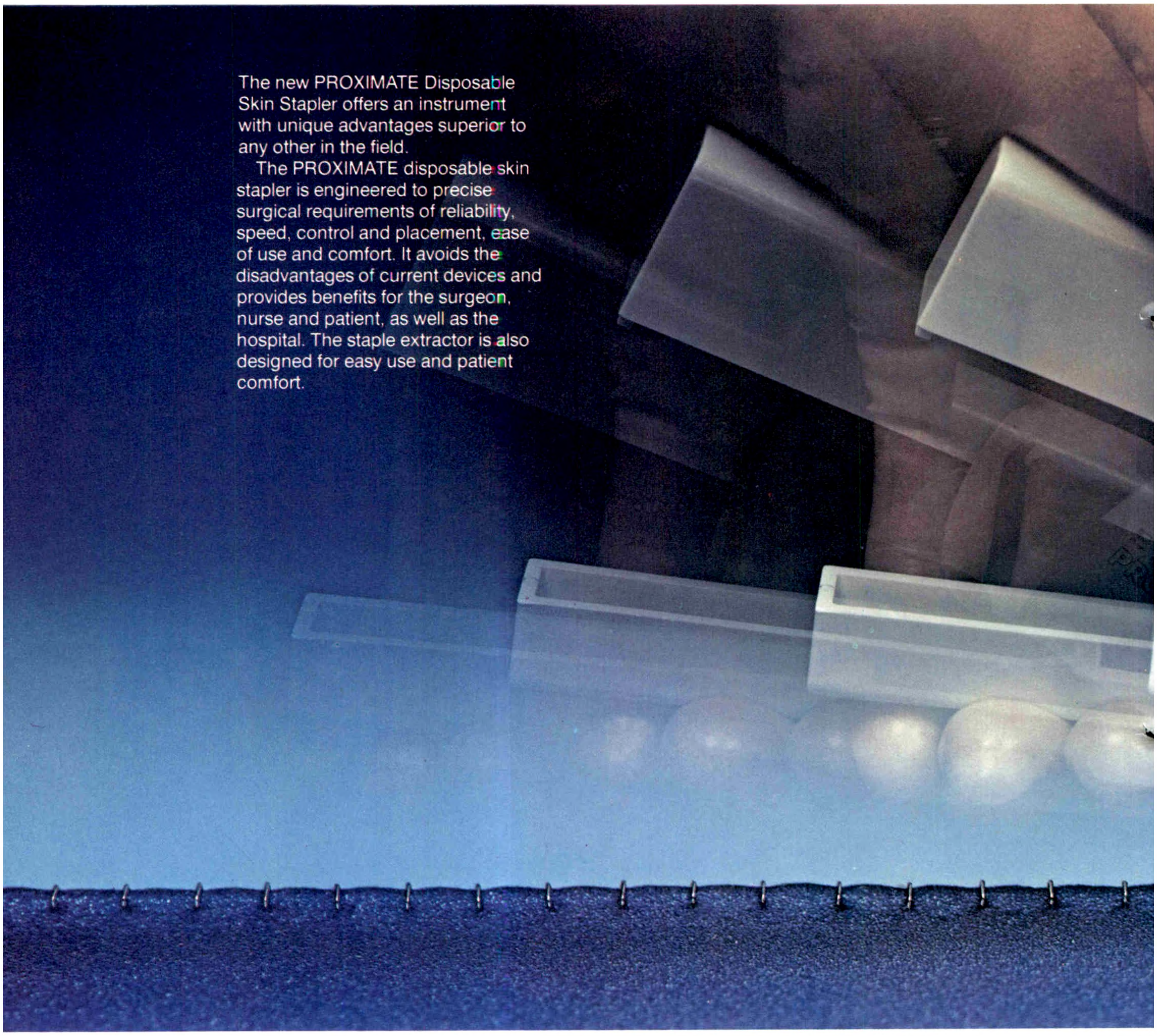
215-643-2600 in Pennsylvania or write Mr. William Taylor at the address below.

NARCO **PILLING**
A Division of Narco Scientific
Delaware Drive
Fort Washington, PA 19034

ETHICON

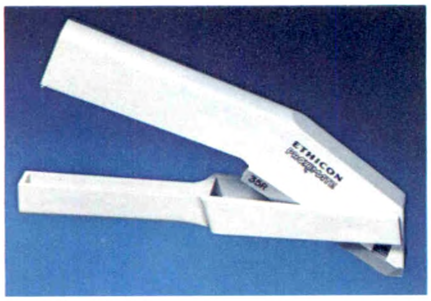
introduces skin stapling for those who do... and those who don't.

PROXIMATE
DISPOSABLE SKIN STAPLER



The new PROXIMATE Disposable Skin Stapler offers an instrument with unique advantages superior to any other in the field.

The PROXIMATE disposable skin stapler is engineered to precise surgical requirements of reliability, speed, control and placement, ease of use and comfort. It avoids the disadvantages of current devices and provides benefits for the surgeon, nurse and patient, as well as the hospital. The staple extractor is also designed for easy use and patient comfort.



RELIABLE

PROXIMATE skin stapler is a single-use, disposable instrument with preloaded staples. Thus it is capable of completing most procedures without the loading or reloading problems of conventional devices. It is always ready for immediate use.

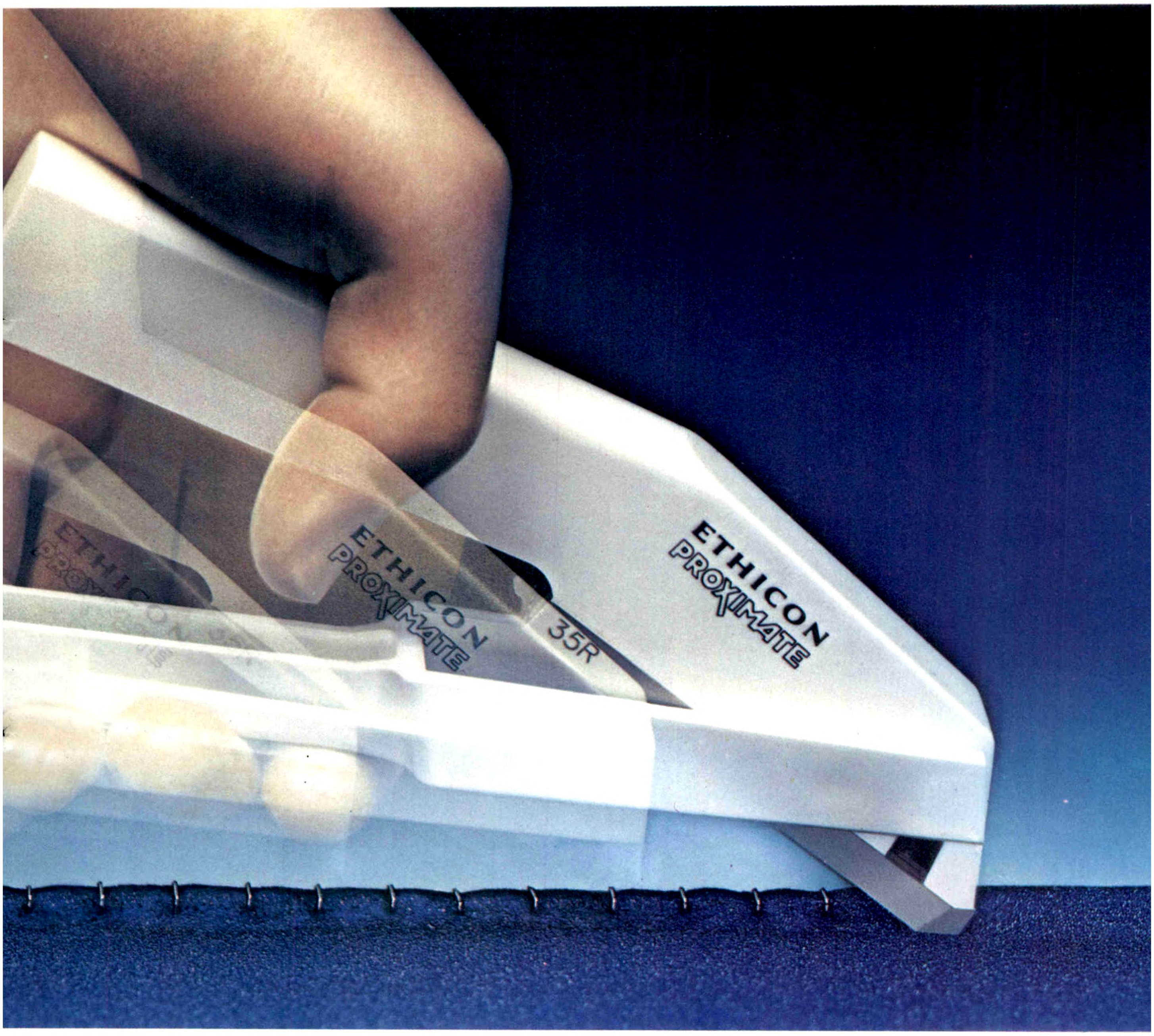
HUMAN ENGINEERED

Made of space-age materials, the PROXIMATE Disposable Skin Stapler weighs much less than conventional skin staplers and requires less force to fire. Minimal weight and force, smooth trigger action and excellent visibility, provides more natural work angles for optimum control and accurate placement.

© ETHICON, Inc. 1978

Trademark

Close and Dispose



FAST

ully automatic. No precocking. No pre-
oading. No waiting for conventional de-
ices in use by other surgeons to be
utoclaved and cooled. You are handed
a fresh, new sterile instrument for your
ersonal use for each procedure, just
ke an ETHICON*needle/suture armed
n a needleholder, ready for use.

NO MAINTENANCE

Unlike reusable devices, the PROXIMATE disposable skin stapler requires no servicing—no time out for repairs, no cleaning, scrubbing, lubricating, wrapping or resterilization.

INEXPENSIVE

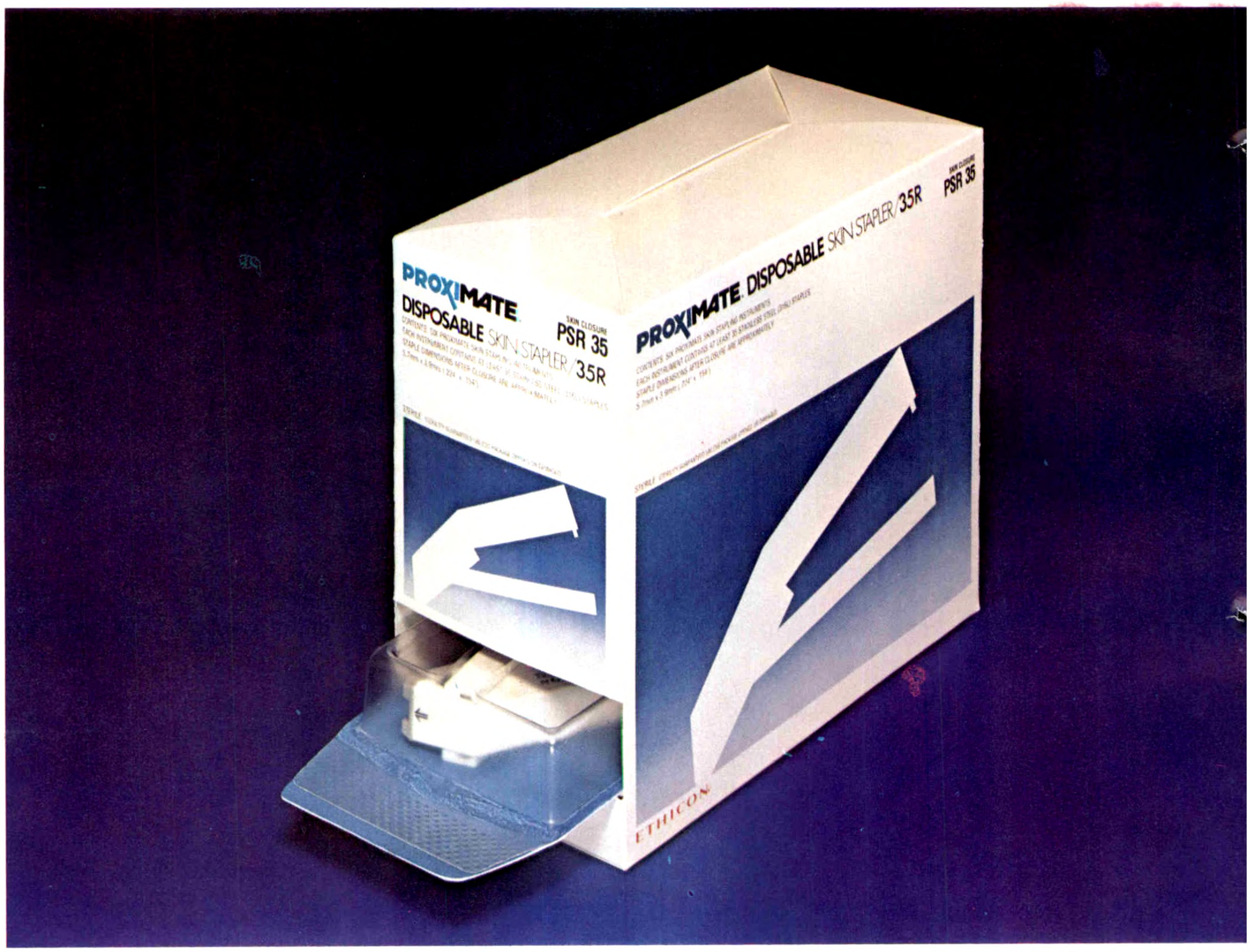
Lower cost per staple and per closure. No initial capital instrument investment. Preloaded with regular or wide staples, the PROXIMATE disposable skin stapler doesn't require the extra cartridges necessary to complete most procedures.

ETHICON
the closing word

PROXIMATE
DISPOSABLE SKIN STAPLER

TREAT IT LIKE A SUTURE

Stored in the OR, so it's always Mayo stand ready for delivery to surgeon. Individually blister-packed, 6 sterile instruments per dispenser box. Choice of regular or wide stainless steel staples.



In the special world of skin closure there is now only one disposable instrument of its kind—the all new PROXIMATE skin stapler.

Your ETHICON Sales Representative will be happy to demonstrate one for you.

ETHICON the closing word

Medical Adrenalectomy with Aminoglutethimide:

Clinical Studies in Postmenopausal Patients with Metastatic Breast Carcinoma

SAMUEL A. WELLS, JR., M.D., RICHARD J. SANTEN, M.D., ALLAN LIPTON, M.D., DARROW E. HAAGENSEN, JR., M.D.
EDWARD J. RUBY, M.D., HAROLD HARVEY, M.D., WILLIAM G. DILLEY, PH.D.

The use of adrenalectomy and hypophysectomy in the management of postmenopausal patients with metastatic breast carcinoma is reserved for highly selected patients. As an alternate approach, a pharmacologic method of inhibiting adrenal cortical secretion was developed which consisted of the daily administration of 1000 mg of aminoglutethimide to block steroidogenesis and either dexamethasone (2.0–3.0 mg/day) or hydrocortisone (40–60 mg/day) as replacement glucocorticoid. This regimen markedly suppressed plasma levels of DHA-S, androstenedione, estrone, and estradiol, and urinary levels of aldosterone. Of 50 patients treated, 19 (38%) demonstrated either a complete (8/19) or a partial (11/19) objective disease remission which lasted for 18.05 ± 3.1 months (mean ± SEM). In 10 (20%) patients, there was stabilization of disease (7.8 ± 1.2 months), accompanied by symptomatic relief of bone pain in six (12%). There was disease progression in 20 (40%) patients. The acute side effects of aminoglutethimide therapy were significant and consisted of transient lethargy (41.5%) and a cutaneous rash (35.8%). Chronic toxicity was negligible. The medical adrenalectomy regimen of aminoglutethimide plus glucocorticoid offers a suitable alternative to surgical adrenalectomy or hypophysectomy in the management of postmenopausal patients with metastatic breast carcinoma.

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina and the Divisions of Endocrinology and Oncology, Department of Medicine and Specialized Cancer Research Center, The Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania

ADRENALECTOMY AND HYPOPHYSECTOMY are surgical procedures widely utilized in the management of postmenopausal women with metastatic breast carcinoma. The reported remission rate for each technique has been in the range of 25–50%.[5,8,9,14] There is an appreciable morbidity and a significant mortality[11,17] associated with these procedures which to some degree has limited their use to highly selected patients. Attempts to suppress ACTH and secondarily adrenal cortical secretion by the administration of high dose corticosteroid therapy have been undertaken; however, regression rates achieved have generally been lower and of shorter duration[6,10] than those resulting from surgical ablative methods. Furthermore, significant adverse side effects accompany the corticosteroid administration.

In 1960, the drug p-(α-amino-phenyl)-α-ethyl glutaramide (aminoglutethimide) was marketed in the United States as an anticonvulsant agent. It was soon apparent clinically, however, that significant side effects were associated with its administration. Approximately 50% of patients taking aminoglutethimide developed a transient morbilliform skin rash. Also some patients developed thyroidomegaly due to a "propylthiouracil-like" effect of the aminoglutethimide which blocked the organification of iodine.[18] The most serious side effect was the occurrence of a marked inhibition of adrenal cortical secretion.[3] Specifically, it was demonstrated that aminoglutethimide blocked the conversion of cholesterol to delta 5-pregnenolone[4] high in the biosynthetic pathway and thus the production of cortisol, androgens and aldosterone. In 1966, aminoglutethimide was recalled from commercial sale; however, it was immediately reinstated as an adrenal inhibitor with an Investigational New Drug status.

In 1969, Griffiths and Hall,[12] appreciating the adrenal cortical inhibiting properties of aminoglutethimide, reported the use of this agent (in doses of 1–2.5 grams/day) in the treatment of nine patients with metastatic

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Supported in part by NIH Contract No. NCI-CB-53851-37, NCI, DHEW, Grant No. 1P30 CA 18450-01 and Grant RR-30 from the General Clinical Resources Center, Program of the Division of Research Resources, National Institutes of Health, Bethesda, Maryland 20014.

0003-4932-78-0500-0475-0105 © J. B. Lippincott Company

carcinoma of the breast. Replacement glucocorticoid (dexamethasone; 0.75 mg/day) and mineralocorticoid (fludrocortisone acetate; 0.1 mg every other day) were also administered concomitantly. Although there was only transient suppression of urinary 17-hydroxycorticoids and 17-ketosteroids during aminoglutethimide therapy, three of their nine patients demonstrated objective tumor remissions persisting for two, seven and nine months. Tumor growth ceased for four and seven months in two other patients. Apparent permanent hypoadrenocorticism was induced in one patient receiving 2.5 g of aminoglutethimide daily, but bilateral adrenal metastases were not excluded.

In 1974, Santen and Lipton[22] further evaluated the aminoglutethimide-dexamethasone regimen and explained why complete adrenal blockade was not observed in previous studies. They demonstrated that aminoglutethimide enhanced the metabolic degradation rate of dexamethasone and thereby reduced its bioavailability. To achieve near-total blockade of adrenal cortical secretion, larger doses of dexamethasone (2–3 mg/day) were required. Unfortunately, the use of the aminoglutethimide-dexamethasone regimen clinically required careful metabolic evaluation of individual patients to determine the ideal dose of dexamethasone relative to aminoglutethimide. It was subsequently demonstrated[23] that hydrocortisone was a more suitable replacement glucocorticoid as its metabolic degradation was uninfluenced by aminoglutethimide.

The purpose of the current study is to report our experience with the aminoglutethimide-glucocorticoid "medical adrenalectomy" regimen in the management of 50 postmenopausal patients with metastatic carcinoma of the breast.

Materials and Methods

Patient Population

Fifty-five patients either from the surgical service at the Duke University Medical Center or from the Divisions of Endocrinology and Oncology at Hershey Medical Center were studied. All of these patients had previously undergone mastectomy for carcinoma of the breast and subsequently developed recurrent disease. Patients were excluded from the study if over 80-years-old, if malignancies of organ systems other than breast were present, or if metastatic breast carcinoma were evident in: more than one-third of the liver, the pulmonary lymphatics, or the central nervous system. Two of the 55 patients were lost to follow, and three were withdrawn from the study because of toxic reactions to the aminoglutethimide. Thus, 50 patients with metastatic breast carcinoma were included in the study, and all were evaluable except one. The relevant clinical data from these patients are presented in Table 1. Of the 50 patients, 35 (70%) had bone metastases, 29 (58%) had skin or soft tissue involvement, 22 (44%) had parenchymal lung involvement, 16 (32%) had liver involvement, and in two (4%) visceral metastases were noted.

Nineteen of the 50 patients when premenopausal had undergone surgical oophorectomy. In 14, the oophorectomy was therapeutic for documented metastatic disease, while in five, the oophorectomy had been "prophylactic."

Criteria of Clinical Response

Classification of a response as an objective complete remission indicated that during therapy all metastatic lesions disappeared for a period of at least three months. A partial regression was defined as a decrease of 50% or greater in the sum of the products of the two largest perpendicular diameters of all measurable lesions, and/or partial recalcification of osteolytic lesions for a period of three months. Regression of osteoblastic lesions or stability with regression of other lesions were also considered objective responses. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in metastatic lesions for at least three months. Progression required an increase of 25% or greater over original measurements.

Prior to therapy and at three monthly intervals thereafter, photographs of skin lesions, and radiographic studies including bone scans, metastatic bone surveys, and liver scans were obtained. Repeat physical examinations were performed on each patient at three monthly intervals, and all data were recorded on a standard patient evaluation flow sheet.

Treatment Protocol

Basal blood samples were collected daily at 8.00–9:00 a.m. for five days prior to the initiation of aminoglutethimide-glucocorticoid therapy. Also during this time, multiple 24 hour urines were collected, and aliquots stored frozen for subsequent hormonal determinations. Additional plasma and urine samples were then obtained at weekly intervals during the first 14 weeks and monthly thereafter until tumor progression was observed.

All patients received at least 250 mg of aminoglutethimide four times daily. In the earliest treated patients, 2 g a day of aminoglutethimide were given. The dexamethasone dosage ranged from 2–3 mg daily. In a selected group of 15 patients, systematic dose response studies were carried out. Dexamethasone was

TABLE 1. *Patients Treated with Aminoglutethimide*

Patient	Months Post-menop.	Dis. Free Interval (mos)	Age (yrs)	Pre-Treatment Involvement					Response	Duration of Response (mos)
				Sk	B	Lg	Lv	Vis		
1	120	24	67	+	–	–	–	–	CR	18
2	0*	9	42	+	–	–	–	–	PR	6
3	84	108	61	+	–	–	–	–	CR	44
4	72	43	59	+	–	–	–	–	CR	12
5	72	24	54	+	+	–	–	–	CR	12
6	60	36	55	+	–	–	–	–	PR	3
7	120	84	57	–	+	+	–	–	PR	9
8	240	78	71	–	+	+	+	–	CR	8
9	60	12	53	–	+	–	+	–	S	7
10	132	84	66	–	+	–	+	–	S	4
11	0	24	47	–	+	–	+	–	CR	40
12	0	3	56	–	+	–	+	–	P	—
13	0	24	44	+	–	+	+	–	P	—
14	120	0	62	+	+	–	–	–	P	—
15	0	24	42	–	–	+	–	–	P	—
16	0	12	49	+	+	+	–	–	S	5
17	96	0	59	+	–	+	+	–	P	—
18	156	20	56	+	+	+	+	–	P	—
19	0	60	51	–	+	–	–	–	P	—
20	460	48	80	+	+	+	+	–	P	—
21	60	108	53	+	–	+	+	–	P	—
22	168	—	67	–	+	–	–	–	Inadequate Follow-up	
23	0	30	49	+	+	–	–	–	P	—
24	0	156	46	–	+	+	+	+	P	—
25	120	72	63	–	–	+	–	–	P	—
26	0	108	43	–	+	–	–	–	CR	30
27	12	0	50	+	+	–	+	–	P	—
28	360	0	76	+	+	–	+	–	S	3
29	84	8	64	+	+	+	+	–	P	—
30	36	12	50	+	–	–	–	–	P	—
31	0	19	50	+	+	+	–	–	PR	18
32	72	36	60	–	+	+	+	–	S	5
33	360	36	74	–	+	–	–	–	S	7
34	0	13	38	+	+	+	–	–	PR	19
35	480	24	79	+	–	+	–	–	CR	21
36	24	0	51	+	+	+	–	–	P	—
37	0	24	45	–	+	–	–	+	PR	8
38	0	28	55	–	+	–	–	–	PR	20
39	0	24	61	+	–	–	–	–	PR	21
40	36	84	50	+	–	–	–	–	P	—
41	0	72	48	–	+	+	–	–	S	23
42	270	60	63	–	+	+	–	–	P	—
43	338	8	55	–	+	+	–	–	S	3
44	0	0	45	–	+	–	–	–	S	14
45	0	24	44	–	+	+	–	–	PR	7
46	168	12	60	+	–	+	–	–	P	—
47	180	36	63	+	+	–	–	–	S	7
48	0	26	49	+	+	–	–	–	PR	19
49	144	16	62	+	+	–	+	–	P	—
50	60	26	59	+	+	–	–	–	PR	11

mos = months, Sk = skin and soft tissue, B = bone, Lg = lung, Lv = liver, Vis = viscera.
* 0 = Therapeutic or prophylactic surgical oophorectomy in premenopausal period.
CR = complete remission, PR = partial remission, S = disease stabilization, P = progression.

given in an initial dose of 2.0 mg daily in four divided doses, and was increased to 2.5 mg daily after two weeks, and then to 3 mg daily after an additional two weeks. Patients were then given 20–30 mg of hydrocortisone daily rather than dexamethasone with dosage increments in a similar fashion at two weekly intervals to a maximum of 60 mg daily. Based upon these studies, the optimum regimen for blocking adrenal steroidogenesis was found to be 40 mg of hydrocortisone (20 mg at bedtime, 10 mg at 0800 hours and 10 mg at 1700 hours), and 250 mg of aminoglutethimide four times daily. The latter dose schedule was used exclusively in patients started on treatment after the dose response studies. Therapy was discontinued in all

TABLE 2. *Patient Response to Aminoglutethimide*

	N	Age (years)	Months Post Menopausal*	Disease Free Interval (mos)	Duration of Response (mos)
Complete Remission	8	60.1 ± 4.3	178.0 ± 66.0	54.1 ± 13.4	25.2 ± 6.3
Partial Remission	11	48.7 ± 2.6	80.0 ± 20.0	28.5 ± 6.0	12.8 ± 2.0†
Stable Disease	10	58.9 ± 3.4	214.6 ± 51.1	29.6 ± 9.3	7.8 ± 1.2†
Disease Progression	20	55.6 ± 2.0	127.6 ± 31.6	36.8 ± 9.4	—

* 19 patients deleted because of surgical oophorectomy performed in premenopausal period.
† $p < 0.02$ compared to Complete Remission.

patients when progression occurred, and chemotherapy or x-ray therapy initiated.

Hormone measurements. Urinary free cortisol was measured by a slightly modified competitive protein binding method of Murphy.[15] Dehydro-epiandrosterone-sulfate (DHA-S) was assayed in unextracted plasma with the radioimmunoassay method of Buster and Abraham.[2] Aldosterone and androstenedione were measured in urine and plasma respectively by radioimmunoassay after extraction and chromatography.[1,21] Thyroxine, TSH and prolactin levels in plasma were determined by double antibody radioimmunoassays using standard techniques.[7,16,25] Dr. John Kendall[19] of the University of Oregon measured ACTH levels in plasma with a previously published method of extraction and radioimmunoassay. Plasma estrone and estradiol were measured after extraction and celite chromatography according to the method of Abraham.[1]

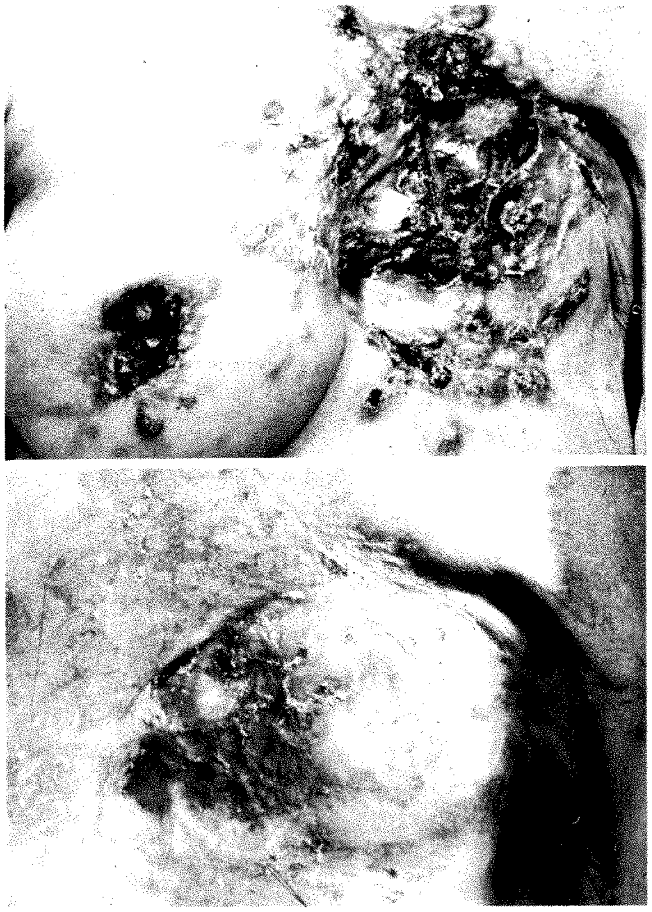


FIG. 1a and b. (a, top) Chest wall, soft tissue, and skin metastases in patient No. 4 prior to therapy. (b, bottom) Appearance of chest wall in the same patient after aminoglutethimide and dexamethasone therapy.

Complete and detailed descriptions of the endocrine methodology and results have recently been published in detail,[20,23-25] consequently the following section describes a brief summary of these aspects.

Statistical Methods

For data evaluation and analysis, Student's t test and the Fisher exact probability test were used.

Results

Clinical Response

Of the 50 patients entered into the study, 8 (16%) underwent complete tumor regression, 11 (22%) demonstrated a partial disease remission, 10 (20%) had stabilization of disease, and 20 (40%) demonstrated disease progression. One patient remained on therapy for only two months, and was not evaluable. There appeared to be no statistically significant difference in patient response relative to age, disease-free interval (from mastectomy to tumor recurrence) or the number of months from menopause to tumor recurrence (Table 2); however, the sample groups were small. There was a statistically significant difference noted, however, between the length of complete (25.2 ± 6.3 months) compared to partial (12.8 ± 2.0 months, $p < .02$) remissions; and between the length of complete remissions compared to the length of disease stabilization (7.8 ± 1.2 months; $p < 0.02$). Of the ten patients who had stabilization of disease, there was marked symptomatic relief of bone pain in six (12%). Examples of the types of responses observed are exhibited in Figures 1–3.

Patient No. 4 (Table 1) primarily had skin and soft tissue metastases (Fig. 1a). After the initiation of aminoglutethimide and dexamethasone, she experi-

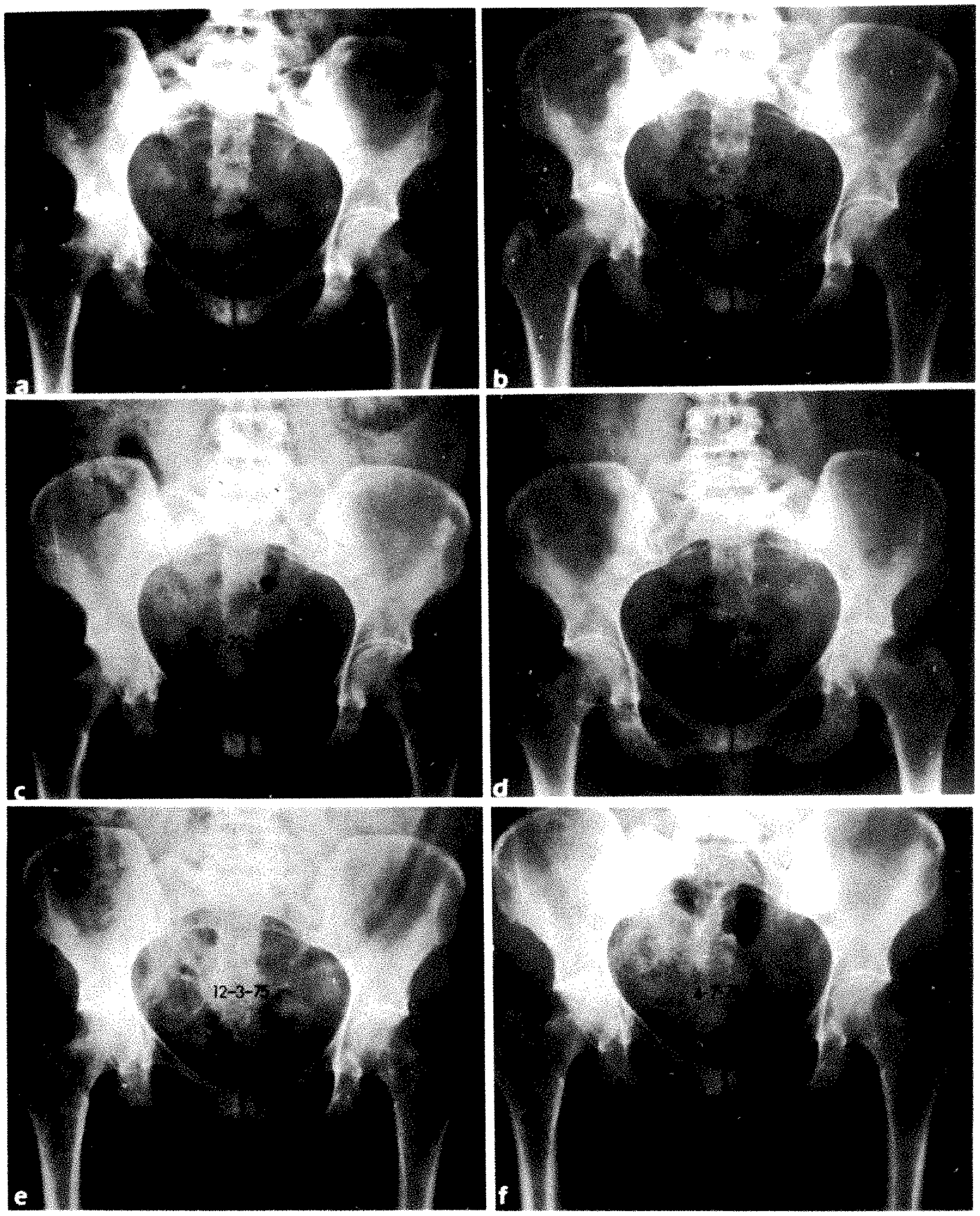


FIG. 2a–f. Pelvic radiographs of patient No. 11 prior to (a) and during (b–f), a prolonged course of aminoglutethimide and dexamethasone therapy.

enced a complete remission (Fig. 1b), which lasted for 12 months.

Patient No. 11 (Table 1) primarily had metastases to bone and liver. After beginning aminoglutethimide and dexamethasone, she underwent a complete remission which has lasted for 40 months. Progressive healing of lytic lesions in the pelvis of this patient is well demonstrated in Figures 2a–f.

Patient No. 35 (Table 1) had breast carcinoma metastatic to skin and lung. Following aminoglutethimide and dexamethasone therapy, she underwent a partial remission which lasted for 20 months. Evidence of this response is demonstrated in Figures 3a–d.

Response to Previous Endocrine Therapy

Thirty-four patients had received one or more forms of hormonal therapy prior to the initiation of the aminoglutethimide-glucocorticoid regimen, *i.e.* high dose corticosteroids (2 patients), oophorectomy (14 patients), hypophysectomy (2 patients), estrogens (17 patients), and/or androgens (23 patients). Of 19 patients who demonstrated a complete or partial remission to aminoglutethimide and glucocorticoid therapy, 12 (61%) had received prior endocrine therapy and a partial or complete remission had resulted in eight (75%). Conversely, of 20 patients who demonstrated

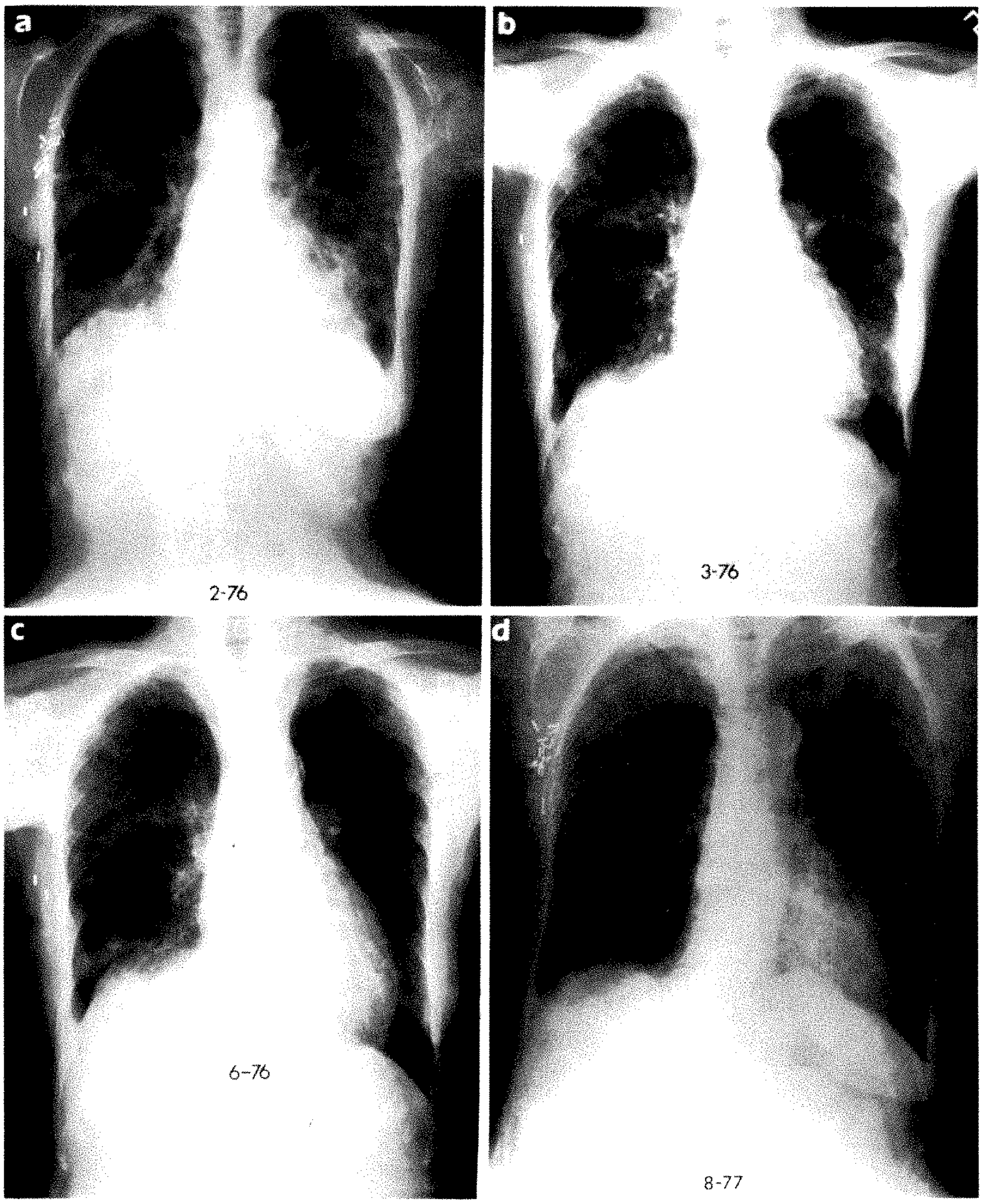


FIG. 3a–d. Chest roentgenographs of patient No. 35 prior to (a) and during (b–d) aminoglutethimide and dexamethasone therapy.

disease progression on aminoglutethimide and dexamethasone therapy, 15 (75%) had received prior endocrine therapy; however, a complete or partial remission had only occurred in three (20%). In our study patients, a previous favorable response to hormonal therapy seemed to predict a subsequent beneficial response to aminoglutethimide plus glucocorticoid ($p < 0.055$).

At the time that this study was begun, estrogen receptor (ER) status was not a criterion for stratification; however, this determination was made in metastatic tumors of six patients, five of which were ER positive. Three of the five patients responded to aminoglutethimide plus a glucocorticoid while the patient who was negative failed to respond.

Hormonal Studies

Evaluation of Plasma DHA-S Levels

Realizing that exogenous hydrocortisone is partially excreted in urine as free cortisol, it was necessary before demonstrating the usefulness of hydrocortisone administration to develop an alternate method of monitoring adrenal function. The measurement of plasma DHA-S was validated by comparing urinary free cortisol and plasma DHA-S levels during dexamethasone and aminoglutethimide administration. The relative suppression of DHA-S and urinary free cortisol was remarkably similar,[24] and, therefore, it was considered valid to monitor adrenal function with DHA-S utilizing hydrocortisone as replacement glucocorticoid.

In 15 patients receiving aminoglutethimide and increasing doses of dexamethasone, the basal DHA-S levels (520 ± 90 ng/ml SEM) progressively fell to a nadir of 68 ± 21 ng/ml during 1000 mg of aminoglutethimide and 3 mg of dexamethasone daily ($p < 0.001$). During chronic therapy with 1000 mg of aminoglutethimide and 40 mg of hydrocortisone, DHA-S levels remained remarkably suppressed to 22.9 ± 5.0 ng/ml ($p < 0.001$). The mean degree of inhibition of DHA-S levels in patients was 93%. Furthermore, during the administration of aminoglutethimide and dexamethasone in eight patients, ACTH levels did not change significantly (64 ± 23 pg/ml) from basal values (81 ± 12 pg/ml). However, during the administration of aminoglutethimide and 40 mg of hydrocortisone, mean ACTH (36 ± 9 pg/ml) was lower than basal values, but remained within the normal range (20–150 pg/ml).

Estrone and Estradiol

In 13 patients receiving 1000 mg of aminoglutethimide and 2 mg of dexamethasone, basal plasma levels of estrone (43.7 ± 11.2 pg/ml) and estradiol (17.5 ± 4.1 pg/ml) fell quite rapidly to levels of 13.5 ± 1.6 pg/ml; $p < 0.02$, and 5.5 ± 1.0 pg/ml; $p < 0.01$ respectively. During prolonged suppression with aminoglutethimide and 40 mg of hydrocortisone, hormone values were further suppressed (estrone 9.3 ± 1.0 pg/ml; $p < 0.001$) and estradiol 5.0 ± 0.5 pg/ml; $p < 0.01$).

Androstenedione

Within two weeks after the initiation of 1000 mg of aminoglutethimide and 2 mg of dexamethasone daily, plasma androstenedione levels significantly increased from basal values of 570 ± 70 pg/ml to 950 ± 160 pg/ml ($p < 0.05$). With the administration of 3 mg of dexamethasone daily, androstenedione levels were suppressed to 340 ± 80 pg/ml ($p < 0.05$) and during chronic treatment with 40 mg of hydrocortisone and 1000 mg of aminoglutethimide daily, plasma androstenedione levels were 230 ± 50 pg/ml; $p < 0.001$.

TSH, Thyroxine and Prolactin

Of 29 patients evaluated during the first eight weeks of therapy, serum thyroxine levels fell by 18% from 8.03 ± 0.57 to 6.79 ± 0.44 ug/dl ($p < 0.01$). Accordingly, TSH levels increased to 178% of control values from 4.47 ± 0.41 uU/ml to 7.91 ± 1.00 ($p < 0.001$). With longer therapy (9–16 weeks) the mean TSH levels rose further to 10.8 ± 2.16 uU/ml. When patients were studied during chronic therapy for up to four years, thyroxine returned toward basal values and demonstration of a significant lowering over basal was no longer possible. The recovery in thyroxine synthesis appeared to result from increased stimulation by TSH which reached levels of 14.5 ± 3.7 uU/ml during chronic therapy. During this observation period, no patients developed clinical evidence of hypothyroidism or goiter.

Mean prolactin levels were in the normal range prior to initiation of therapy (21.5 ± 2.6 ng/ml), and no significant increase could be demonstrated during the 14 weeks when patients were receiving 1000 mg of aminoglutethimide and increasing doses of dexamethasone and hydrocortisone respectively.

Side Effects of Aminoglutethimide

The major side effects of aminoglutethimide therapy are a transient cutaneous rash and dose dependent CNS soporific effects. A morbilliform skin rash usually occurs within 10–14 days after initiation of aminoglutethimide therapy and is frequently associated with malaise and fever. With continuation of treatment, the cutaneous rash spontaneously disappears and patients on chronic therapy rarely have persistence of this complication after the first two to three weeks of therapy. The CNS effects are similar to those induced by the sleeping pill glutethimide (Doriden®) and include lethargy, ataxia, and dizziness. The CNS side effects are also transient, and almost always resolve after one to six weeks of therapy. Furthermore, they are dose related and are not common with the administration of 1000 mg of aminoglutethimide a day.

Of the 49 patients evaluable in our study, 22 (41.5%) experienced significant lethargy, 19 (35.8%) developed a transient cutaneous rash, 6 (11.3%) developed transient ataxia, and 5 (9.4%) complained of dizziness. Three patients (5.8%) noted nystagmus and hyponatremia was detected in two patients (3.8%). Two patients in our study developed an excoriative dermatitis and a third patient developed extreme lethargy early in the treatment course. These side effects resolved, however, following cessation of drug therapy. Compared to the acute effects (Table 3) of aminoglutethimide therapy, the chronic effects were almost nonexistent, there being no lethargy, skin rash, ataxia or nystagmus. Five patients complained of facial fullness, three of weight gain, and two patients experienced leg cramps.

TABLE 3. *Acute and Chronic Aminoglutethimide Toxicity*

	Lethargy	Skin Rash	Ataxia	Other
Acute	22/53 (41.5%)	19/53 (35.8%)	6/53 (11.3%)	5/53 (9.4%)*
Chronic	0/49	0/49	0/49	9/49 (18.5%)†

* Dizziness.

† Weight gain (5), facial fullness (3), leg cramps (2).

When evaluating the incidence of acute side effects of aminoglutethimide therapy, it was evident that patients who experienced either a partial or complete remission had a significantly higher incidence ($p < 0.01$) of a cutaneous rash (10/19; 54%) than did those patients who experienced tumor progression (5/20; 25%). Such an association, however, was not noted with either ataxia, dizziness, or lethargy.

No attempt was made to continue metabolic studies after the cessation of aminoglutethimide therapy in patients with progressive disease. However, no evidence of adrenal cortical insufficiency was noted in any patient. Adrenal tissue during treatment was available for histological examination in patient No. 8. She died acutely of a probable myocardial infarction during the eighth month of aminoglutethimide and dexamethasone therapy. At postmortem examination, her adrenal cortex appeared normal, both grossly and histologically (Fig. 4).

Discussion

Although surgical adrenalectomy and hypophysectomy have been effective in inducing disease remission in postmenopausal women with recurrent breast carcinoma, the associated morbidity accompanying these procedures is appreciable and there is a significant mortality. Furthermore, the nonsurgical methods of suppressing adrenal cortical secretion such as the administration of high dose corticosteroids have only limited effectiveness and carry an appreciable morbidity for the patient.

The described "medical adrenalectomy" regimen of 1000 mg of aminoglutethimide and 2–3 mg of dexamethasone, or preferably 40 mg of hydrocortisone, appears to have great utility in managing postmenopausal patients with metastatic breast carcinoma. It has been demonstrated by our studies that this drug combination markedly suppresses adrenal cortical secretion with significant reductions in the plasma levels of estrone, estradiol, DHA-S, aldosterone, and androstenedione. In our evaluation of 50 patients, 19 (38%) demonstrated a complete or partial objective remission during therapy. These results compare favorably with those obtained in other series[6,11] reporting the utility of surgical adrenalectomy in the treatment of patients with metastatic breast carcinoma.

There are several advantages to this proposed drug therapy which should be stressed. The combination of 1000 mg of aminoglutethimide and 40 mg of

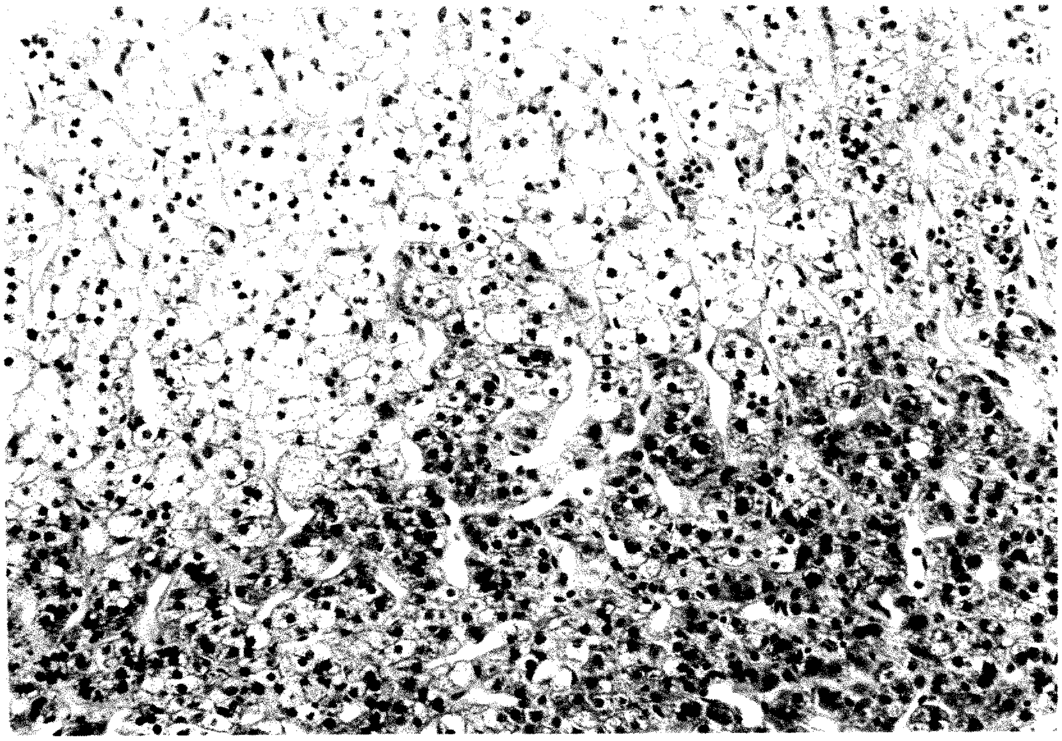


FIG. 4. Histologic section of the adrenal cortex in patient No. 8 who died suddenly of a probable myocardial infarction during aminoglutethimide and dexamethasone therapy. Hematoxylin and eosin ×100.

hydrocortisone administered orally is a simple regimen which can be used easily by primary care physicians. Since there is no drug interaction occurring between aminoglutethimide and hydrocortisone, one can reliably depend on these agents to induce adrenal cortical suppression. Whereas surgical adrenalectomy is an irreversible procedure requiring permanent mineralocorticoid and glucocorticoid replacement, such is not the case in patients treated with aminoglutethimide and hydrocortisone. The adrenal suppression in almost all cases is reversible and maintenance steroid therapy is not required after cessation of treatment. This is of a particular advantage if subsequent chemotherapy or radiation therapy are to be instituted since the addisonian state complicates the administration of these therapeutic modalities.

As demonstrated, there was an early increase in plasma androstenedione after the initiation of aminoglutethimide and dexamethasone. This was followed by a subsequent reduction in androstenedione levels with higher dosages of dexamethasone and even further suppression with the administration of hydrocortisone. The increase in androstenedione was temporally related to suppression of plasma estrone and estradiol levels. It has been demonstrated[13] that the main source of estrone and estradiol in postmenopausal women is the conversion of androstenedione into estrone in peripheral tissues by a process referred to as aromatization. It has also been shown that aminoglutethimide is a potent inhibitor of the aromatization of androstenedione to estrone[27] in placental microsome preparations. Our findings of an increase in androstenedione levels associated with a concomitant reduction of plasma estrone could be explained by an inhibiting effect of aminoglutethimide on peripheral aromatization. It is possible that the clearance of androstenedione is reduced or the metabolism of estrone increased to account for these findings; nonetheless, our data suggest that in many instances estrogen production is inhibited before total adrenal blockade is accomplished. This would be a potentially beneficial side effect of aminoglutethimide therapy in addition to its adrenocortical suppressive effects.

There was some concern that the goitrogenic effect of aminoglutethimide administration would cause an increase in plasma TSH levels and concomitantly elevated prolactin levels. Since it had been demonstrated by other investigators[27] that prolactin exerts a potential stimulatory effect on breast tumor growth, such an effect would be deleterious. As demonstrated by our findings, mean prolactin levels were not elevated in the subjects treated with aminoglutethimide and glucocorticoid replacement.

Significant side effects were demonstrated in a large percentage of patients during the first few weeks of treatment. Aminoglutethimide had to be withdrawn from three of the original 55 patients because of a severe drug rash in two and marked lethargy in one. A significant proportion of patients also experienced ataxia and nystagmus. Conversely, after the first two weeks of therapy and during the chronic administration of aminoglutethimide and hydrocortisone, there were minimal side effects. The drug rash spontaneously disappeared in the large majority (17/19) of patients with continuation of aminoglutethimide. A small number of patients on chronic therapy complained of weight gain and facial fullness. Approximately 20% of the patients in our group required mineralocorticoid replacement therapy primarily due to the marked suppression of plasma aldosterone levels.

With the recent availability of a technique for determining estrogen and progesterone receptors in the cytosol of breast carcinoma cells, it appears that an even greater selection factor can be exerted to determine which patients might be responsive to hormonal therapy. Our studies demonstrate that the "medical adrenalectomy" regimen of aminoglutethimide plus hydrocortisone provides remission rates similar to those obtained with surgical adrenalectomy. Currently, we are conducting a randomized trial of evaluating these two procedures in the management of postmenopausal patients with metastatic carcinoma of the breast.

References

1. Abraham, G. E. and Chakmakjian, Z. H.: Serum Steroid Levels During the Menstrual Cycle in a Bilateral Adrenalectomized Woman. J. Clin. Endocrinol. Metab., 37:581, 1973.
2. Buster, J. E. and Abraham, G. E.: Radioimmunoassay of Plasma Dehydroepiandrosterone Sulfate. Analyt. Letters, 5:543, 1972.
3. Camacho, A. M., Brough, A. J., Cash, R. and Wilroy, R. S.: Adrenal Toxicity Associated with the Administration of an Anticonvulsant Drug. J. Paediatr., 68:852, 1966.
4. Cash, R., Brough, A. J., Cohen, M. N. P. and Satoh, P. S.: Aminoglutethimide (Elipten—Ciba) As an Inhibitor of Adrenal Steroidogenesis: Mechanism of Action and Therapeutic Trial. J. Clin. Endocrinol. Metab., 27:1239, 1967.
5. Daicoff, G. R., Harmon, R. and Van Prohaska, J.: Effects of Adrenalectomy on Mammary Carcinoma. Arch. Surg., 85:800, 1962.
6. Dao, T. L. Y., Tan, E. and Brooks, V.: A Comparative Evaluation of Adrenalectomy and Cortisone in the Treatment of Advanced Mammary Carcinoma. Cancer, 14:1259, 1961.
7. Demers, L. M., Abt, W. J. and Krieg, A. F.: A New Combined Thyroid Hormone Index Based on Thyroxine, Triiodothyronine and Resin Uptake. Am. J. Clin. Pathol. 65:356, 1976.
8. Edelstyn, G., Gleadhill, C. and Lyons, A.: Total Hypophysectomy for Advanced Breast Cancer. Clin. Radiol., 19: 426, 1968.
9. Forrest, A. P. M.: Endocrine Treatment of Breast Cancer. Israel J. Med. Sci., 1:259, 1965.
10. Forrest, A. P. M., Benson, E. A., Ker, H., et al. Controlled Studies in Advanced Breast Cancer. *In* Forrest, A. P. M. and Kunkler, P. B. (eds.) Prognostic Factors in Breast Cancer, Edinburgh: Livingstone, 1968.

11. Fracchia, A. A., Randall, H. T. and Farrow, J. H.: The Results of Adrenalectomy in Advanced Breast Cancer in 500 Consecutive Patients. Surg. Gynecol. Obstet., 125: 747, 1867.
12. Griffiths, C. T., Hall, T. C., Saba, Z., et al.: Preliminary Trial of Aminogluethtimide in Breast Cancer. Cancer, 32:31, 1973.
13. Grodin, J. M., Siiteri, P. K. and MacDonald, P. C.: Source of Estrogen Production in Postmenopasual Women. J. Clin. Endocrinol. Metab., 36:207, 1973.
14. Hellstrom, J. and Franksson, C.: Adrenalectomy in Cancer of the Breast. *In* Currie, A. R. and Illingsworth, C. F. W. (eds.) Endocrine Aspects of Breast Cancer, p. 5, Edinburgh: Livingstone, 1958.
15. Murphy, B. P., Engleberg, W. and Pattee, C. J.: Simple Method for the Determination of Plasma Corticoids. J. Clin. Endocrinol. Metab., 23:293, 1963.
16. Odell, W. D., Wilbert, J. F. and Paul, W. E.: Radioimmunoassay of Thyrotopin in Human Serum. J. Clin. Endocrinol. Metab., 25:1179, 1965.
17. Pearson, O. H. and Ray, B. S.: Results of Hypophysectomy in the Treatment of Metastatic Mammary Carcinoma. Cancer, 12:85, 1959.
18. Rallison, M. L., Tyler, F. H. and Kumagi, L. F.: Goitrous Hypothyroidism Induced by an Anticonvulsant Drug. J. Paediatr., 65:1085, 1964.
19. Rees, L. H., Cook, D. M., Kendall, J. W., et al.: A Radioimmunoassay for Rat Plasma ACTH. Endocrinology, 89: 254, 1971.
20. Samojlik, E., Santen, R. J. and Wells, S. A.: Adrenal Suppression with Aminoglutethimide. II. Differential Effects of Aminoglutethimide on Plasma Androstenedione and Estrogen Levels. J. Clin. Endocrinol. Metab., 45:480, 1977.
21. Sampson, E. J., Derck, D. D. and Demers, L. N.: Comparison of Two Radioimmunoassay Kits for Aldosterone Determination. Clin. Biochem., 9:216, 1976.
22. Santen, R. J., Lipton, A. and Kendall, J.: Successful Medical Adrenalectomy with Aminoglutethimide: Role of Altered Drug Metabolism. JAMA, 230:1661, 1974.
23. Santen, R. J., Wells, S. A., Runic, S., et al.: Adrenal Suppression with Aminoglutethimide. I. Differential Effects of Aminoglutethimide on Glucocorticoid Metabolism as a Rationale for Use of Hydrocortisone. J. Clin. Endocrinol. Metab., 45:469, 1977.
24. Santen, R. J., Wells, S. A., Cohn, M., et al.: Compensatory Increase in TSH Secretion Without Effect on Prolactin Secretion in Patients Treated with Aminoglutethimide. J. Clin. Endocrinol. Metab., 45:739, 1977.
25. Santen, R. J., Samojlik, E., Lipton, A., et al.: Kinetic, Hormonal, and Clinical Studies with Aminoglutethimide in Breast Cancer. Cancer, 39:2948, 1977.
26. Smithline, F., Sherman, L. and Kolodny, H. D.: Prolactin and Breast Carcinoma. N. Engl. J. Med., 292:784, 1975.
27. Thompson, E. A., Jr. and Siiteri, P. K.: Utilization of Oxygen and Reduced Nicotinamide Adenine Dinucleotide Phosphate by Human Placental Microsomes During Aromatization of Androstenedione. J. Biol. Chem., 249:5364, 1974.

DISCUSSION

DR. J. SHELTON HORSLEY, III (Richmond, Virginia): At the Medical College of Virginia, under the direction of Drs. Heber H. Newsome and Peter W. Brown, we have taken a little different approach.

(Slide) The objective of our study was to compare the response to medical adrenalectomy with subsequent surgical adrenalectomy.

(Slide) Twenty-two patients were treated by medical adrenalectomy, as Dr. Wells has outlined. Six patients who did not respond, subsequently had bilateral surgical adrenalectomy. None of these showed any response. The 16 patients who did respond to medical adrenalectomy over a period of three months all responded to surgical adrenalectomy.

We have had limited experience using this drug over a long period of time. If Dr. Wells' program continues to show these excellent results, surgical adrenalectomy for metastatic breast carcinoma may be a thing of the past.

At the present time, we are using it as a "predictor". We don't have any delusions that the 100% accuracy will continue, but it's very exciting that we seem to have a "predictor" that can give us much better results than any other criteria available.

I would like to ask Dr. Wells two questions. First, is there any correlation between response to medical adrenalectomy and the presence of estrogen receptors in the breast cancers of his patients? Secondly, after the patients have been on medical adrenalectomy, do they exhibit any change in tolerance to subsequent chemotherapy?

PRESIDENT SCOTT: Are there other discussants? (No one responded.) If not, I'd like to ask one question of Dr. Wells which is a little bit aside from the thrust of this particular paper, but that is: What about commenting, Dr. Wells, on the role of aminoglutethimide in Cushing's disease and in primary aldosteronism, if you would do so?

Would you close?

DR. SAMUEL ALONZO WELLS, JR. (Durham, North Carolina): In regard to Dr. Horsley's question, we did not use estrogen receptor status to stratify patients preoperatively and this was primarily for two reasons. At the time that this study was initiated the clinical utility of estrogen receptor analysis was not clarified and, furthermore, this assay was not available commercially. Also, in patients with metastatic breast carcinoma it is often difficult to obtain adequate tissue at the time of disease recurrence.

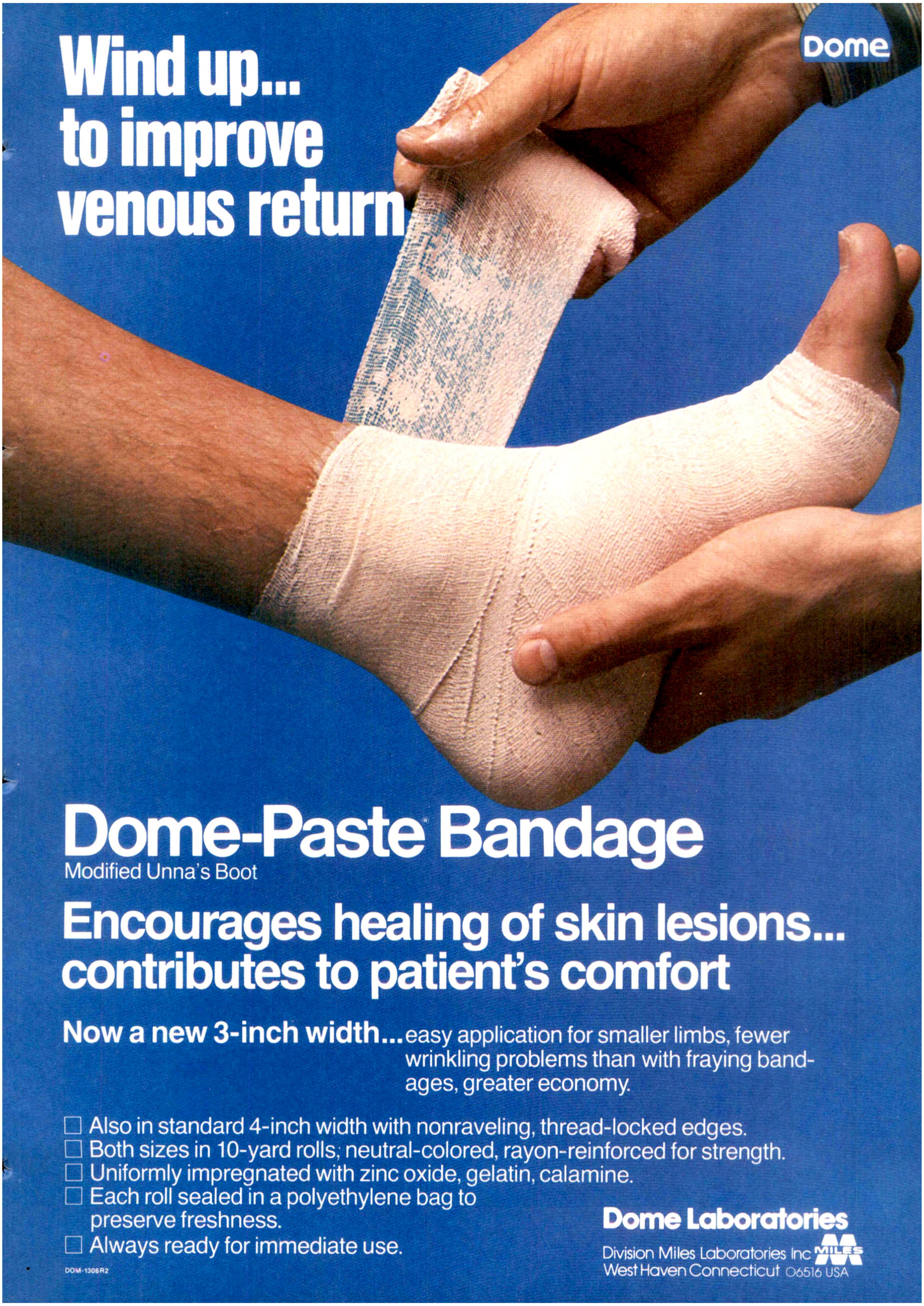
Approximately 11 months ago we began a randomized study comparing the efficacy of surgical adrenalectomy to the aminoglutethimide glucocorticoid medical adrenalectomy regimen in postmenopausal patients with metastatic carcinoma of the breast. Every attempt is made to obtain metastatic breast tumor for estrogen receptor determination and all patients who are estrogen receptor negative are excluded from this study. I think that there is no question that the estrogen receptor protein determination is a pivotal test regarding the decision to use hormonal therapy or chemotherapy.

In regard to your second question, we did not notice that there was any effect of the aminoglutethimide glucocorticoid regimen on subsequent chemotherapy. Some of these patients, 34 to be precise, had some hormonal therapy prior to the time that they started on the aminoglutethimide glucocorticoid regimen. Those patients who had previously responded to a hormonal regimen had a greater incidence of complete or partial remission than did those patients who had not had a previous response to hormonal therapy.

Regarding Dr. Scott's question, I think that aminoglutethimide has some use in patients with certain forms of adrenocorticohyperplasia. It has certainly been used in selected patients with Cushing's syndrome, but probably has been most effective in subjects with aldosteronomas.

This drug has also been used to treat patients who have inappropriate ACTH secretion from various malignant tumors. Large doses of this drug have to be given to achieve adrenal blockade, but it has been effective in certain instances.

It certainly appears that aminoglutethimide has usefulness medically, and if the proper regimen is given, it is competitive with other hormonal ablative techniques in the management of patients with metastatic carcinoma of the breast.



Dome

Wind up... to improve venous return

Dome-Paste® Bandage

Modified Unna's Boot

Encourages healing of skin lesions... contributes to patient's comfort

Now a new 3-inch width... easy application for smaller limbs, fewer wrinkling problems than with fraying bandages, greater economy.

☐ Also in standard 4-inch width with nonraveling, thread-locked edges.
☐ Both sizes in 10-yard rolls; neutral-colored, rayon-reinforced for strength.
☐ Uniformly impregnated with zinc oxide, gelatin, calamine.
☐ Each roll sealed in a polyethylene bag to preserve freshness.
☐ Always ready for immediate use.

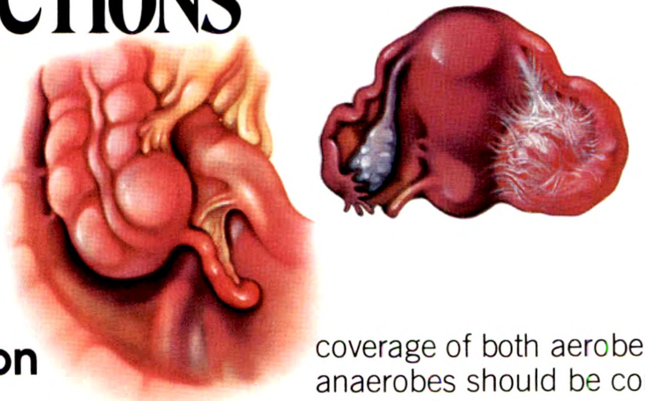
Dome Laboratories

Division Miles Laboratories Inc MILES
West Haven Connecticut 06516 USA

DOM-1306R2

Upjohn

THE BIPHASIC NATURE OF SERIOUS INTRA-ABDOMINAL/PELVIC INFECTIONS



Introduction

The biphasic clinical nature of serious intra-abdominal and female pelvic infections may be related to sequential dominance first of aerobes and then of anaerobes. Antimicrobial coverage of both aerobes and anaerobes should be considered during all stages of serious intra-abdominal and female pelvic infections.

The majority of these infections are polymicrobial. During the early, toxic phase, aerobes are

Acute Phase:
Peritoneal Response

Peritoneal contamination with polymicrobial (aerobic and anaerobic) flora from the bowel or vagina may occur during surgery or as a result of trauma, septic abortion, or perforating diseases such as appendicitis.

Clinical signs in the acute phase include increasing abdominal tenderness and fever. Bacteremia, which may progress to septic shock, occurs fairly frequently. In female pelvic infections, bacteremia and septic pelvic thrombophlebitis are always a threat because of the rich vasculature of the female pelvis.

Initially, antimicrobial therapy directed against aerobes such as *Escherichia coli* often results in defervescence and clinical improvement. Failure of the patient to respond or recurrence of symptoms may indicate anaerobic involvement. *B. fragilis* is the anaerobe most frequently isolated in patients with intra-abdominal sepsis or serious female pelvic infections.

© 1978 The Upjohn Company

Late Phase:
Peritoneal Response

The clinical course may progress to walling off of the infection and subsequent abscess formation. These collections of pus can be located intraperitoneally, retroperitoneally, or within the viscera.

Progression from peritonitis to abscess formation may be an insidious process or may be marked by sudden deterioration of the patient who had been recovering. At this point, failure to respond to appropriate antibiotic therapy should alert the clinician to the possibility of intra-abdominal or pelvic abscess formation and generally the dominant pathogens; the coexistent anaerobes may contribute to the clinical picture. In the patient who progresses to the late phase and develops an abscess, anaerobes (especially *Bacteroides fragilis*) are the dominant isolates.

the potential need for operative intervention.

In both the early peritonitis stage and the later abscess stage, culture of purulent material yields aerobes and anaerobes in the majority of instances. In fact, anaerobes have been isolated from 90% to 96% of intra-abdominal infections associated with bowel perforation. Anaerobes such as *B. fragilis* have been isolated in 80% to 100% of patients with pelvic abscesses studied with appropriate techniques of specimen collection and culture.

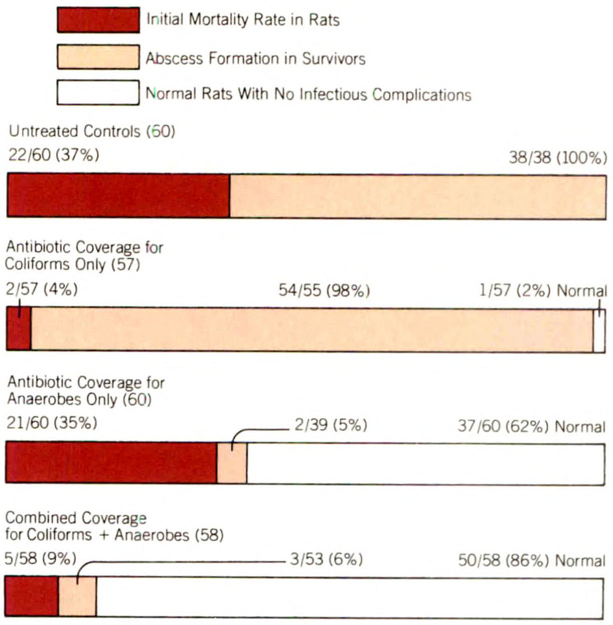
For information about one antibiotic to consider in treating serious infections due to anaerobic pathogens, please turn the page.

Upjohn

INDUCED PERITONEAL SOILAGE

The sequence of events that follow experimental induction of peritoneal soilage in rats parallels the biphasic course of this disease. Although animal data cannot be directly applied to humans, this model helps explain the pathogenesis.

A standardized inoculum of rat colonic contents containing both aerobic and anaerobic organisms was implanted into the peritoneal cavity of male Wistar rats. The animals were observed for response and survivors were sacrificed after ten days. The rats developed a two-stage disease: initial, acute peritonitis and later, intra-abdominal abscesses. Mortality and progression of these stages varied sharply with antimicrobial coverage for aerobes, anaerobes, or both.



In this study, coliform organisms appeared to be responsible for the early mortality associated with fecal peritonitis, whereas *B. fragilis* and other anaerobes were associated with later abscess formation.

Upjohn

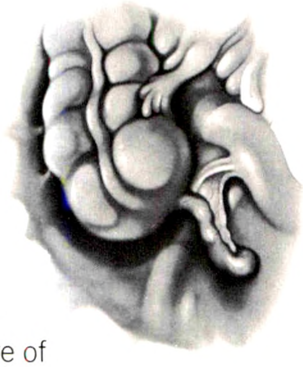
THERAPEUTIC CONSIDERATIONS...

Anaerobic activity

Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious ntra-abdominal and female pelvic infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection; serious lower respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; and serious skin and soft-tissue infections caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, in vitro dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should



consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Indications include: serious lower respiratory tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances, the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible in vitro and were successfully eradicated from the clinical lesions.

Other therapeutic considerations

1. Cleocin PO_4 (clindamycin phosphate injection) is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section of the brief summary on the following page.

> If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

---

*Clostridia are more resistant than most anaerobes to clindamycin. Some species, eg, *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative. MED B-5-S J-6219-9

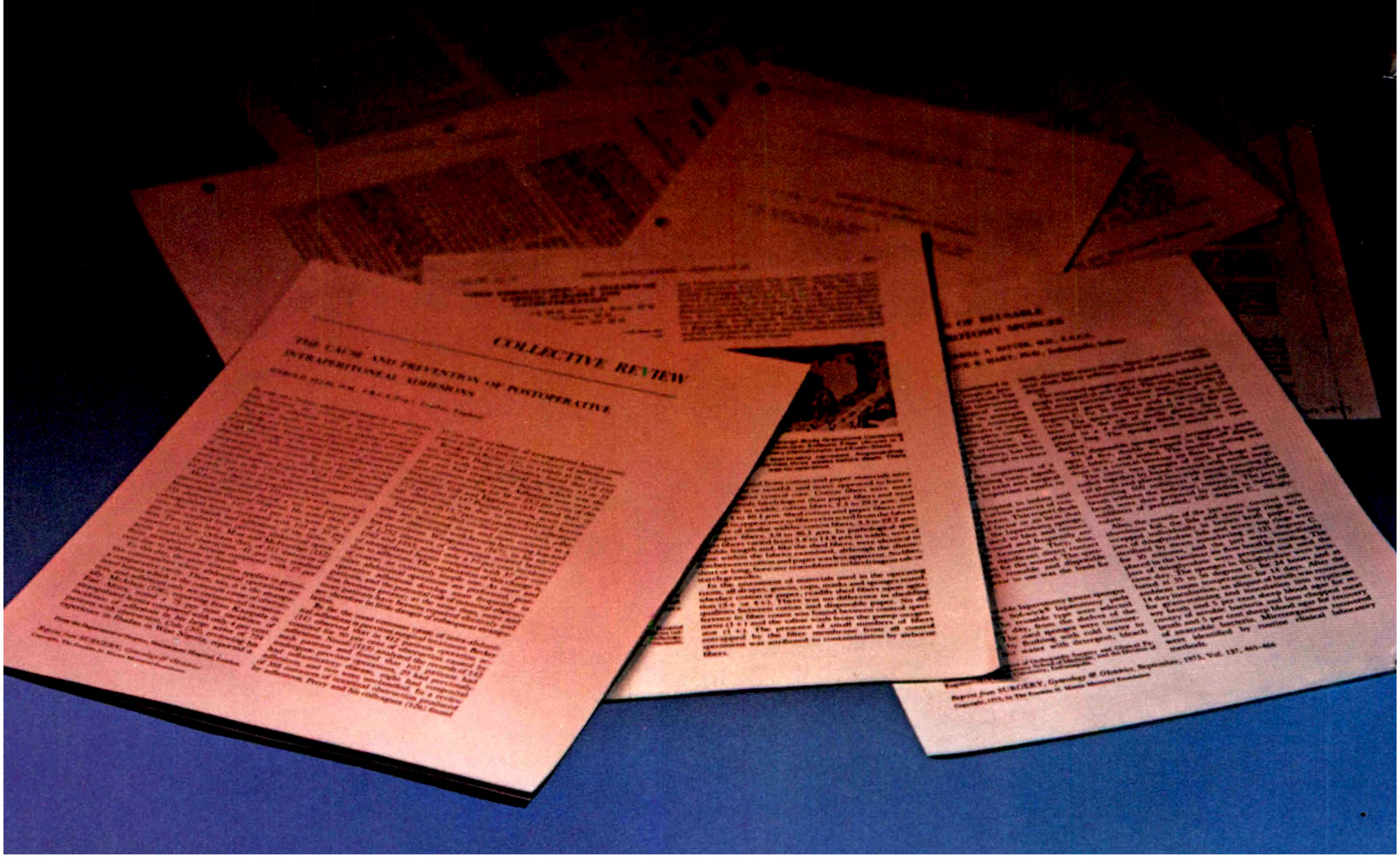
STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

FOR OVER 20 YEARS CLINICAL LITERATURE HAS IDENTIFIED LINT AS A POTENTIAL CAUSE OF POSTSURGICAL COMPLICATIONS.


COLLECTIVE REVIEW
THE CAUSE AND PREVENTION OF POSTOPERATIVE INTRAPERITONEAL ADHESIONS

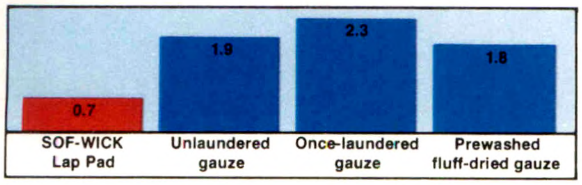
Reaction to lint left in the operative site is not rare. Numerous reports in clinical literature confirm this. For example:

In 1955, Amromin et. al. reported on 65 patients and concluded, "Merely sponging an open wound with cotton gauze . . . may be sufficient to deposit enough lint to cause postoperative complications."[1] More recently, Sturdy et. al. discovered traces of gauze in granulomas removed from 23 out of 28 patients who had undergone prior surgery.[2] During the 1970s, Ellis et. al. discovered lint in 27% of 309 repeat laparotomies.[3]

SOF-WICK® Lap Pad helps reduce a potential source of foreign body reactions.

SOF-WICK Lap Pad reduces a potential cause of granulomas, adhesions and intestinal obstruction. The unique fabric sheds far less lint than gauze and eliminates pilling and fraying associated with gauze lap sponges.

Comparative Quantities of lint (milligrams)[4]



Helps maintain a clearer, drier operative site.

Highly absorbent SOF-WICK Lap Pad wicks blood considerably faster than gauze.

Developed to minimize tissue and organ trauma.

Unique SOF-WICK Lap Pad fabric is demonstrably softer than gauze and conforms for easy packing or walling off.

Decreases risk of contamination.

Single-use, X-ray detectable SOF-WICK® Lap Pad is guaranteed sterile by Johnson & Johnson. Available in convenient PATIENT-READY® Sterile packs of five pads — in four sizes: 14″ × 14″, 9″ × 9″, 28″ × 6″, 14″ × 3″.

References:

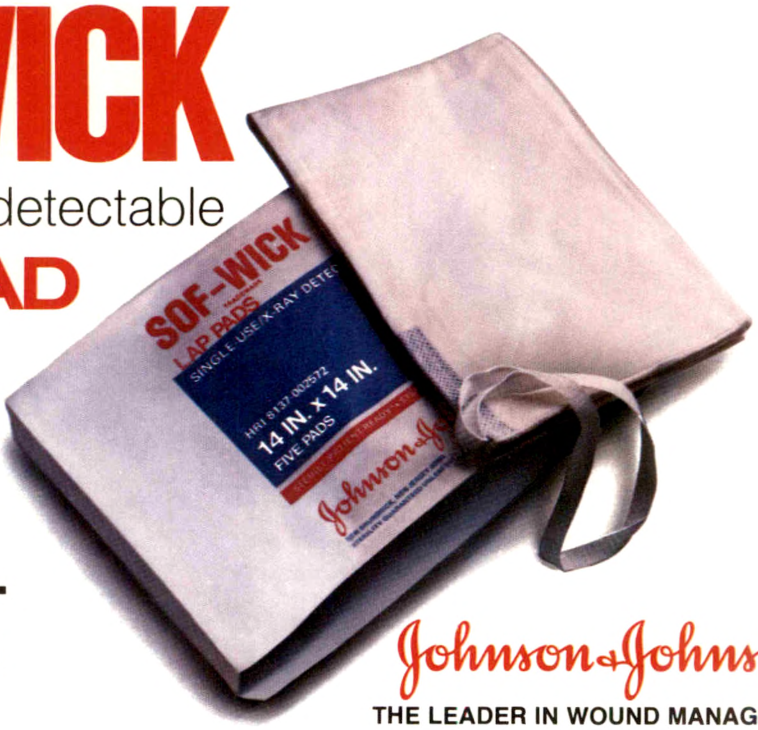
1. Amromin G, Saphir O, Goldberger I: Lint granuloma. *Arch Pathol* 60:467-71, 1955.
2. Sturdy JH, Baird RM, Gerein AN: Surgical sponges: a cause of granuloma and adhesion formation. *Ann Surg* 165:128-134, 1967.
3. Ellis DM: The cause and prevention of postoperative intraperitoneal adhesions. *Surg Gynec & Obst* 133:497-511, 1971.
4. Average test data on file, Johnson & Johnson Research.

SOF-WICK

TRADEMARK

single use/x-ray detectable

LAP PAD

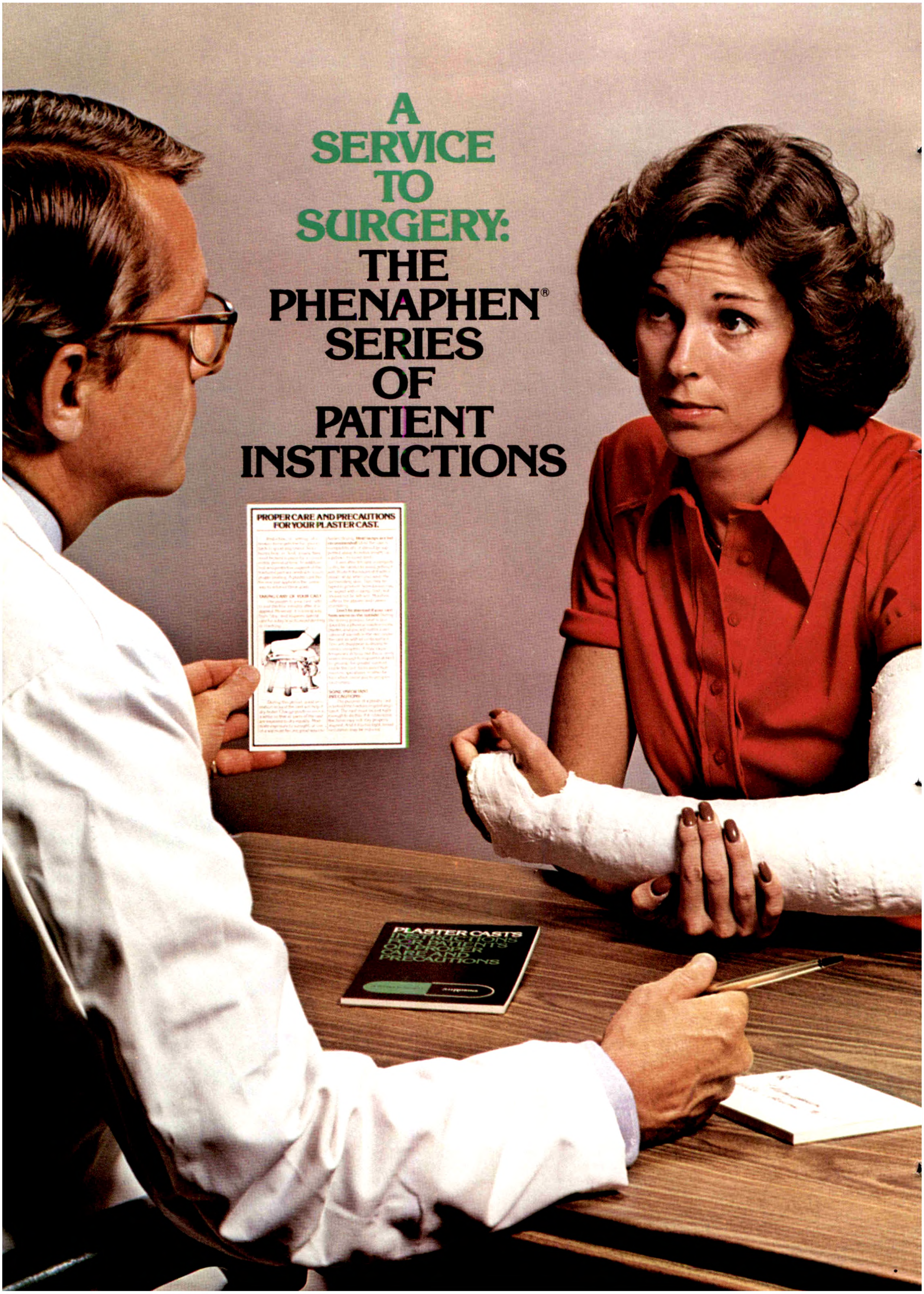


Different from Gauze... for a Reason

Johnson & Johnson

THE LEADER IN WOUND MANAGEMENT.

A SERVICE TO SURGERY: THE PHENAPHEN® SERIES OF PATIENT INSTRUCTIONS


PROPER CARE AND PRECAUTIONS FOR YOUR PLASTER CAST.
PLASTER CASTS
INSTRUCTIONS FOR PATIENTS ON PROPER CARE AND PRECAUTIONS

PRACTICAL ADVICE

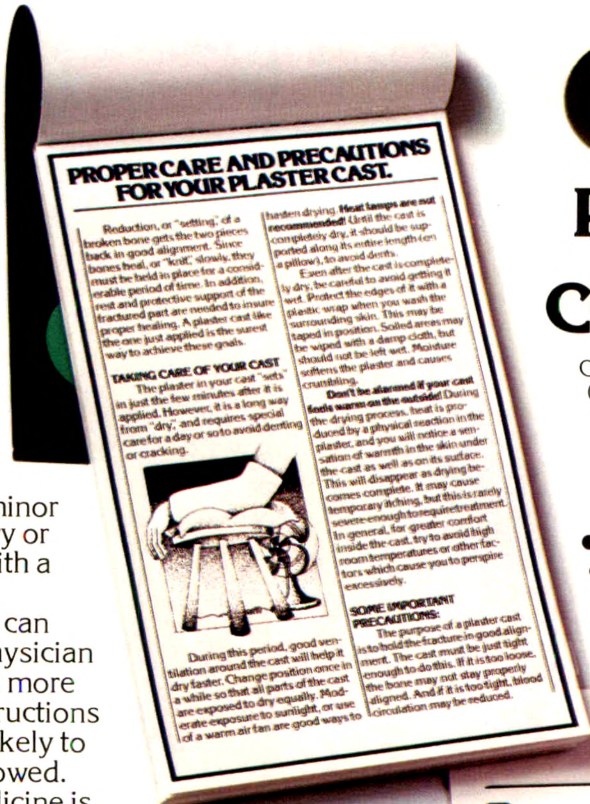
At A. H. Robins, we believe that making it easier for the patient to follow your instructions is just as much our obligation as providing you with useful pharmaceutical products.

And making it easier—for both of you—is the whole idea of this first in a series of Phenaphen Patient Pads: convenient, preprinted instructions ready for you to tear off and personalize with any minor changes you feel necessary or desirable for the patient with a plaster cast.

Informative patient aids can reduce legal risks for the physician as much as 50%.* But even more important, when your instructions are written, they're more likely to be remembered...and followed. And that's what good medicine is all about.

To order a supply of these pads, write "Phenaphen Casts Pad" on your Rx blank and mail to: Phenaphen Service to Surgery, A. H. Robins Company, 1407 Sherwood Avenue, Richmond, Va. 23220.

*Patient Care, 7:4, pp. 119-27, Feb. 15, 1973.



PROPER CARE AND PRECAUTIONS FOR YOUR PLASTER CAST.

Reduction, or "setting," of a broken bone gets the two pieces back in good alignment. Since bones heal, or "knit," slowly, they must be held in place for a considerable period of time. In addition, rest and protective support of the fractured part are needed to insure proper healing. A plaster cast like the one just applied is the surest way to achieve these goals.

TAKING CARE OF YOUR CAST

The plaster in your cast "sets" in just the few minutes after it is applied. However, it is a long way from "dry," and requires special care for a day or so to avoid denting or cracking.

During this period, good ventilation around the cast will help it dry faster. Change position once in a while so that all parts of the cast are exposed to dry equally. Moderate exposure to sunlight, or use of a warm air fan are good ways to hasten drying. **Heat lamps are not recommended!** Until the cast is completely dry, it should be supported along its entire length (on a pillow), to avoid dents.

Even after the cast is completely dry, be careful to avoid getting it wet. Protect the edges of it with a plastic wrap when you wash the surrounding skin. This may be taped in position. Soiled areas may be wiped with a damp cloth, but should not be left wet. Moisture softens the plaster and causes crumbling.

Don't be alarmed if your cast feels warm on the outside! During the drying process, heat is produced by a physical reaction in the plaster, and you will notice a sensation of warmth in the skin under the cast as well as on its surface. This will disappear as drying becomes complete. It may cause temporary itching, but this is rarely severe enough to require treatment. In general, for greater comfort inside the cast, try to avoid high room temperatures or other factors which cause you to perspire excessively.

SOME IMPORTANT PRECAUTIONS:

The purpose of a plaster cast is to hold the fracture in good alignment. The cast must be just tight enough to do this. If it is too loose, the bone may not stay properly aligned. And if it is too tight, blood circulation may be reduced.

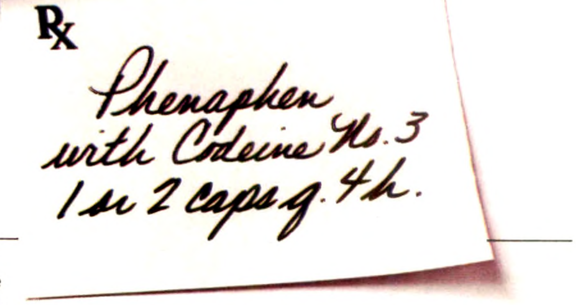
POTENT ANALGESIA

PHENAPHEN® WITH CODEINE No. 3

Codeine Phosphate, USP—30 mg
(Warning: May be habit-forming)
Acetaminophen, USP—325 mg

"The black and green capsule with codeine."

- A pharmaceutically elegant capsule
- Easier to swallow than a tablet
- Economical for the patient



Rx

Phenaphen
with Codeine No. 3
1 or 2 caps q. 4h.

Phenaphen® with Codeine No. 2

Codeine Phosphate, USP—15 mg
(Warning: May be habit-forming)
Acetaminophen, USP—325 mg

Phenaphen® with Codeine No. 3

Codeine Phosphate, USP—30 mg
(Warning: May be habit-forming)
Acetaminophen, USP—325 mg

Phenaphen® with Codeine No. 4

Codeine Phosphate, USP—60 mg
(Warning: May be habit-forming)
Acetaminophen, USP—325 mg

Indications: Phenaphen with Codeine No. 2 and Phenaphen with Codeine No. 3 are indicated for the relief of mild to moderate pain. Phenaphen with Codeine No. 4 is indicated for the relief of moderate to severe pain.
Contraindications: Hypersensitivity to acetaminophen or codeine.
Warnings: *Drug dependence.* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients. Caution patients that acetaminophen and codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants. Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) may exhibit additive CNS depression; when used together reduce dose of one or both.

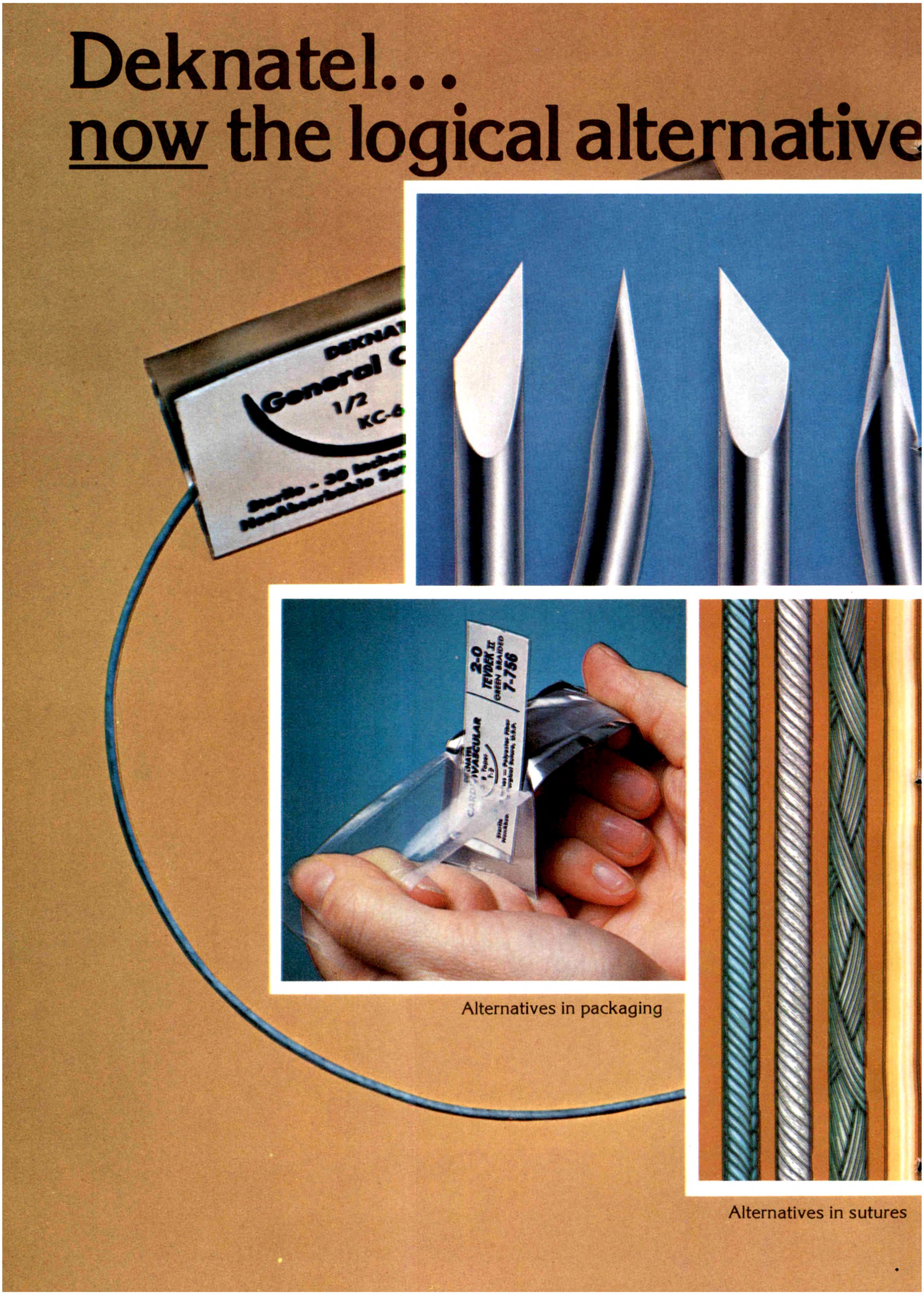
Usage in Pregnancy. Safe use is not established. Should not be used in pregnant patients unless potential benefits outweigh possible hazards.
Precautions: *Head injury and increased intracranial pressure.* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal condition. Acetaminophen and codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients. Administer with caution to elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.
Adverse Reactions: Most frequent are lightheadedness, dizziness, sedation, nausea, and vomiting; more prominent in ambulatory than in nonambulatory patients; some may be alleviated if patient lies down; other: euphoria, dysphoria, constipation and pruritus.
Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings.

For symptoms and treatment of overdosage and full prescribing information, see product literature.

A·H·ROBINS
A. H. Robins Company, Richmond, Va. 23220
Member of Certified Medical Representatives Institute.



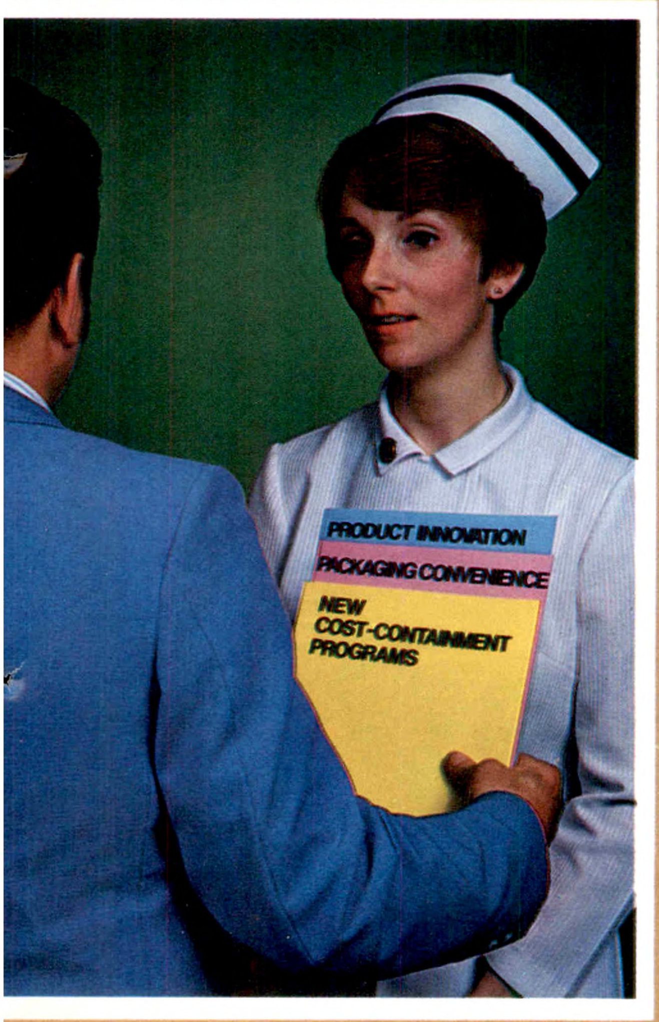
Deknatel…
now the logical alternative

Alternatives in packaging

Alternatives in sutures

or your surgery

ternatives in needles

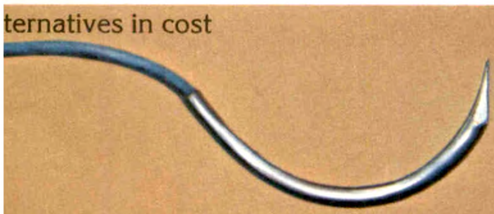


Why now?

Because of new leadership to enhance our proven skills. Renewed emphasis on new product development. And added resources available to us from Howmedica. Result? An accelerated commitment to meet your needs better than ever before. With logical alternatives. In exclusive needles — such as the All-Purpose 'K' Needle®. In quality sutures — such as time-tested silk, preferred for over 50 years, unique Tevdek®, and Polydek®. And in new cost-containment programs to help control the level of spending in your OR.

Needle exclusivity, time-tested suture quality, cost-containment . . . all good reasons to make Deknatel your logical alternative in wound management. And there are others. Why not let your Deknatel sales representative help you select the product alternatives most logical for your surgery?

ternatives in cost



the logical alternative
in wound management

DEKNATEL

Queens Village, New York 11429
A DIVISION OF HOWMEDICA, INC.
© 1978 DEKNATEL

INFECTION!
-a "dirty" word to surgeons...

...'ANCEF' helps "clean up" the site

'ANCEF' Offers Broad Coverage

of the major areas of post-surgical infection due to susceptible indicated organisms. See Indications on next page.

High Levels Present in Tissues and Fluids*

'Ancef' achieves high concentrations (relative to MIC levels for most indicated organisms) in bone, synovial fluid, skin and soft tissues (such as pleural fluid and lymph nodes). 'Ancef' is also excreted in a microbiologically active form in urine.

High and Prolonged Serum Levels

A single 1 gram IV injection produced a mean peak concentration of 'Ancef' of 190 mcg/ml in healthy adult volunteers. After 4 hours, levels of 16.5 mcg/ml were still present.

Because of its long half-life, generally 'Ancef' may be given every 8 hours.

Most infections can be treated with 500 mg to 1 gram every 8 hours.

Well Tolerated

- Infrequent phlebitis
- No nephrotoxicity reported to date. (Transient rises in serum BUN, SGOT, SGPT and alkaline phosphatase have been reported without clinical evidence of renal or hepatic damage.)

Use with caution in patients with penicillin allergy or other allergies. For further information on contraindications, warnings, precautions and adverse reactions, see brief summary of prescribing information on next page.

*Data on file, SK&F Medical Department. Tissue penetration is regarded as essential to therapeutic efficacy, but specific antibiotic tissue levels have not been directly correlated with specific therapeutic effects.

ANCEF® IV/IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

SK&F

a SmithKline company

ANCEF® IV IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

Most infections can be treated with 500 mg to 1 gram every 8 hours.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Ancef® (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus (Diplococcus) pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus.*

Septicemia due to *Str. pneumoniae, S. aureus* (penicillin-sensitive and penicillin-resistant), *P. mirabilis, E. coli,* and *Klebsiella* species.

Endocarditis due to *S. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

Contraindications: 'Ancef' is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Antibiotics, including 'Ancef', should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Usage in Pregnancy — Safety of this product for use during pregnancy has not been established.

Usage in Infants — Safety for use in prematures and infants under one month of age has not been established.

Precautions: Prolonged use of 'Ancef' may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to adults or children with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions in the package literature).

A false-positive reaction for glucose in the urine may occur with Clinitest® tablets; use glucose enzyme-type reagents.

Adverse Reactions: The following reactions have been reported: Drug fever, skin rash, vulvar pruritus, eosinophilia, neutropenia, leukopenia, thrombocythemia, and positive direct and indirect Coombs tests have occurred. Transient rise in SGOT, SGPT, BUN, and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment. Nausea, anorexia, vomiting, diarrhea, and oral candidiasis (oral thrush) have been reported. Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

Administration and Dosage: 'Ancef' may be administered intramuscularly or intravenously after reconstitution. See the package literature for reconstitution procedures.

See the package literature for dosage recommendations.

How Supplied: 'Ancef' (sterile cefazolin sodium, SK&F) — supplied in vials equivalent to 250 mg., 500 mg. or 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 500 mg. or 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

Smith Kline &French Laboratories
Philadelphia, Pa.

SK&F
a SmithKline company

Staging Laparotomy in Hodgkin's Disease

WILLIAM R. SANDUSKY, M.D., ROBERT C. W. JONES, JR., M.D.,† J. SHELTON HORSLEY, III, M.D.,*
WILLIAM L. MARSH, JR., M.D., THOMAS W. TILLACK, M.D., CHARLES J. TEGTMEYER, M.D.,
CHARLES E. HESS, M.D.

Staging laparotomy was performed at the University of Virginia Medical Center on 111 patients with Hodgkin's disease. The operation included multiple liver and lymph node biopsies and, excepting three patients, splenectomy. The histopathology was reviewed and the 111 patients were classified as follows: nodular sclerosis, 74; mixed cellularity, 28; lymphocyte predominance, 7; and undetermined, 2. There were no deaths. Wound, pulmonary or urinary tract complications occurred in 11 patients. One case of postoperative thrombophlebitis occurred and in another case small bowel obstruction developed, and resolved without reoperation. The pathologic stage (PS) following laparotomy was unchanged from the clinical stage (CS) in 64%, reduced in 20%, and advanced in 16%. The therapy, however, was altered in 38% of the patients. Lymphangiography in 103 patients was interpreted as showing lymph node involvement in 38, equivocal involvement in 11, and no involvement in 54. Among the 92 examinations reported as either positive or negative, 77% were confirmed histopathologically, 21% were falsely positive, and 2% were falsely negative. The spleen was positive for Hodgkin's disease in 39% of cases, and in these patients with positive spleens there was no reason to suspect intra-abdominal involvement preoperatively in 21%.

From the Departments of Surgery, Pathology, Radiology and Medicine, University of Virginia Medical Center, Charlottesville, Virginia

TRADITIONALLY, THE FUNCTION OF THE SURGEON in Hodgkin's disease has been to obtain tissue for pathologic examination, or, rarely, to resect localized disease.

The observations of an interdisciplinary group at the Stanford University Medical Center[2,4] begun in the 1960's have now expanded the surgical role to include assessment of the presence or absence of the process within the abdominal cavity and, if present, its extent.

In 1969, stimulated by the work in progress at Stanford and other institutions, laparotomy was introduced as a part of the Hodgkin's disease staging protocol at the University of Virginia Medical Center.

Patients and Methods

Clinical Staging

Clinical staging (CS)[3] in patients with histopathologically documented Hodgkin's disease included a history with special attention to fever, night sweats and weight loss; physical examination with special attention to all peripheral lymph node chains, liver, spleen, and bony tenderness; chest roentgenograms and whole lung tomography if mediastinal and/or hilar adenopathy was present; complete blood counts with differential and platelet count; erythrocyte sedimentation rate; liver function tests: PPD skin testing with anergy determination if indicated; bilateral lower extremity lymphangiography; and bone marrow biopsy. Optional studies included radioisotopic scans and in cases where liver involvement was suspected, liver biopsy either percutaneous or under direct vision at laparoscopy. On the basis of these studies each patient was given a clinical stage.

Pathological Staging (PS)[3]

A staging laparotomy was next recommended on all patients except for those in whom stage IV disease was established or apparent, or in whom a major diagnostic operation was considered ill-advised because of the patient's general health status. Based on these laparotomy findings each patient is given a final pathological stage.

Operative Technique

The operative incision varied with the preference of the surgeon. A left paramedian rectus muscle retracting incision was used in 62% of the patients, and in one instance was combined with a lateral transverse extension. The midline approach was employed in 36%; in the remaining two patients a left subcostal incision was used.

Initially a complete intra-abdominal exploration was carried out. Open wedge biopsies were taken from the anterior edge of the right and left lobes of the liver and deeply from the liver substance using a

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

* Present address: Division of Surgical Oncology, Medical College of Virginia, Richmond, Virginia.

† Dr. Jones was Clinical Fellow of the American Cancer Society 1976–1977.

0003-4932-78-0500-0485-0075 © J. B. Lippincott Company

TABLE 1. *Clinical Stage Compared with Pathological Stage*

Clinical stage	Pathological Stage IA	IB	IIA	IIB	IIIA	IIIB	IVB	IIA_E	$IIIB_E$	
IA	13				6					19
IB		2				2				4
IIA			18		4					22
IIB				8		1	1			10
IIIA	4		9		14					27
IIIB				1		7	2			10
IVB		1				4	6			11
IIA_E								2		2
IIB_E									1	1
$IIIA_E$			1					1		2
	17	3	28	9	24	14	9	3	1	108*

* Three other patients are not included in this table. Two were in complete clinical remission at the time of laparotomy. In one, disease was found in the spleen; in the other, no disease was found. The third patient although in clinical remission at the time of laparotomy, had a positive lymphangiogram (CS IIA) but no disease was found at laparotomy.

biopsy needle. Additionally, any focal involvement or suspicious area was biopsied.

Access to the paraaortic area was gained by dividing the ligament of Treitz, retracting the retroperitoneal duodenum cephalad and incising the posterior peritoneum along the left side of the aorta to the level of the bifurcation. This permitted visualization of nodes along the left side of the aorta and on the right between the aorta and vena cava, and provided access to the iliac nodes. Grossly abnormal paraaortic or iliac lymph nodes were readily identified and were excised either singly or in groups of nodes. When grossly abnormal nodes were obtained further search for nodes was abandoned. If no enlarged nodes were apparent the preoperative lymphangiogram was an invaluable guide to node sampling. Lymph nodes that were positive or equivocal on lymphangiogram were exised. Metallic clips were used to obtain hemostasis and to serve as radiopaque markers. Intraoperative x-rays were obtained to identify the site of the excised node and to ascertain whether or not the desired node had been obtained, but the search was not concluded until the abnormal-appearing lymph node had been removed. If there were no questionable nodes, either on inspection or on preoperative lymphangiogram, several single nodes or a short chain of nodes lying along the left side of the aorta were excised. Other sampling was directed at nodes in the region of the celiac axis, the porta hepatis, the mesentery, near the tail of the pancreas, and in the splenic hilum; nodes in the latter region frequently accompanied splenectomy.

Splenectomy was accomplished after dividing the short gastric vessels, the splenocolic ligament and the posterior peritoneal attachments of the spleen. The splenic artery and vein were divided and ligated individually. For purposes of subsequent radiographic identification, several metallic clips were placed on the splenic pedicle. The splenic bed was not drained routinely. Bone marrow biopsy was performed as a part of the preoperative clinical staging but in a few instances when preoperative specimens were not entirely satisfactory an open biopsy from the ilium was performed.

Transposition of the ovaries was not a part of the initial staging protocol but in more recent staging operations it was offered to women of reproductive age and younger. The appendix was removed in 71 patients. Other incidental procedures, when indicated, were carried out; these included tubal ligation in five; cholecystectomy in two; renal cystectomy in two; umbilical hernioplasty in one; excision of liver hemangioma in one, and uterine dilatation and curretage in one.

Closure of the abdominal incision also varied with the preference of the surgeon but in all instances interrupted nonabsorbable suture material was used for the principal fascial layers. Systemic prophylactic antibiotics were administered to 13 patients but the remaining ones received none.

Results

During the period from April 1969 through June 1977, 111 patients with histopathologically verified Hodgkin's disease had a staging laparotomy performed at the University of Virginia Hospital. Ages ranged from five to 72 years; 60 were males and 51 were females; 105 were white and six were black.

Histopathological Subclassification

The original microscopic slides and/or additional sections from the paraffin blocks were available for review in all 111 cases. The slides were reviewed separately and independently by two of us (WLM and TWT), without knowledge of the original histopathological subclassification. Lesions were classified according to the criteria of Lukes[7] and the Rye Conference[6] on Hodgkin's disease as follows: nodular sclerosis (NS), 74; mixed cellularity (MC), 28; lymphocyte predominance (LP), 7; lymphocyte depletion (LD), none; undetermined, 2.

The Effect of Laparotomy on Staging

Table 1 compares the clinical stage determined by the preoperative clinical staging evaluation with the final pathological stage determined by laparotomy.

The information in this table is summarized in Figure 1. The clinical stage was unchanged in 71 patients (63.9%), reduced in 22 (19.8%), and advanced in 18 (16.2%).

Complications

There were no deaths. However, early or late postoperative complications did occur in 13 patients as follows: superficial wound infection in four patients, superficial wound infection and urinary tract infection in one, superficial wound infection and pneumonia in one, deep wound infection in one, pneumonia in three, atelectasis and pleural effusion in one, thrombophlebitis in one, and partial small bowel obstruction (at four and six months following operation) in one patient.

The deep wound infection occurred in an obese male with a thick abdominal panniculus in whom lateral transverse extension of the left paramedian incision was necessary to obtain adequate exposure. On the seventh day following operation purulent material was evacuated from the deep fascia; culture yielded *Basteroides fragilis* in large numbers. An incidental appendectomy had been performed during the staging laparotomy. Immediate recovery occurred without other untoward events and the patient tolerated a full course of radiation therapy. An incisional hernia developed later.* Complications in all other patients including the one patient with thrombophlebitis and the one with small bowel obstruction resolved without residual stigmata.

Lymphangiography

Bipedal lower extremity lymphangiography was performed in 103 patients. These studies were interpreted as positive in 38 patients, equivocal in 11, and negative in 54. Among the 92 examinations reported unequivocally as positive or negative, 77.1% were confirmed histopathologically, while 20.6% were falsely positive and 2.1% falsely negative.

Splenic Involvement

Splenectomy was performed in 108 patients, and was positive for Hodgkin's disease in 42 (38.8%). Of the three patients who did not have splenectomy, two had gross involvement of the liver at laparotomy and one had a negative exploration with a small grossly normal spleen.

The weights of the positive spleens are compared with the negative ones in Figure 2. It is of interest to note that there is considerable variability in the size of the uninvolved spleens and that many small spleens were positive for Hodgkin's disease.

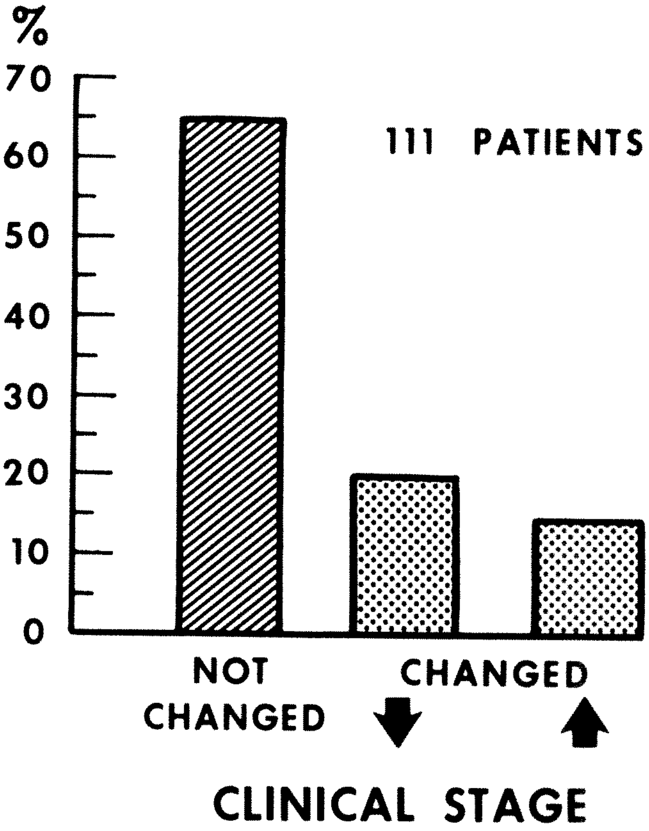


FIG. 1. Comparisson of the clinical stage, determined by preoperative evaluation, with the pathological stage, determined by laparotomy.

Splenic palpability on physical examination depends not only on the size of this organ but also on the habitus of the patient and the skill of the examiner. Preoperatively the spleen could be felt in 18 patients; in eight of these the spleen was histopathologically positive for Hodgkin's disease and in ten negative. Of the 90 patients with nonpalpable spleens, 34 were histopathologically positive and 56 were negative. Thus, the physical examination is not a reliable indicator of splenic involvement with Hodgkin's disease.

Radioisotopic scanning of the spleen was done preoperatively in only 12 patients, too few in number to draw conclusions. Four tests were positive and confirmed histopathologically, four were negative and confirmed, and four were falsely negative. There were no falsely positive scans.

The spleen was positive in nine patients in whom there had been no reason to suspect intra-abdominal pathology on the basis of preoperative evaluation. In each of these patients the spleen was not palpable (one also had a negative splenic scan), the liver was

---

* Since presentation of this paper the hernia has been successfully repaired.

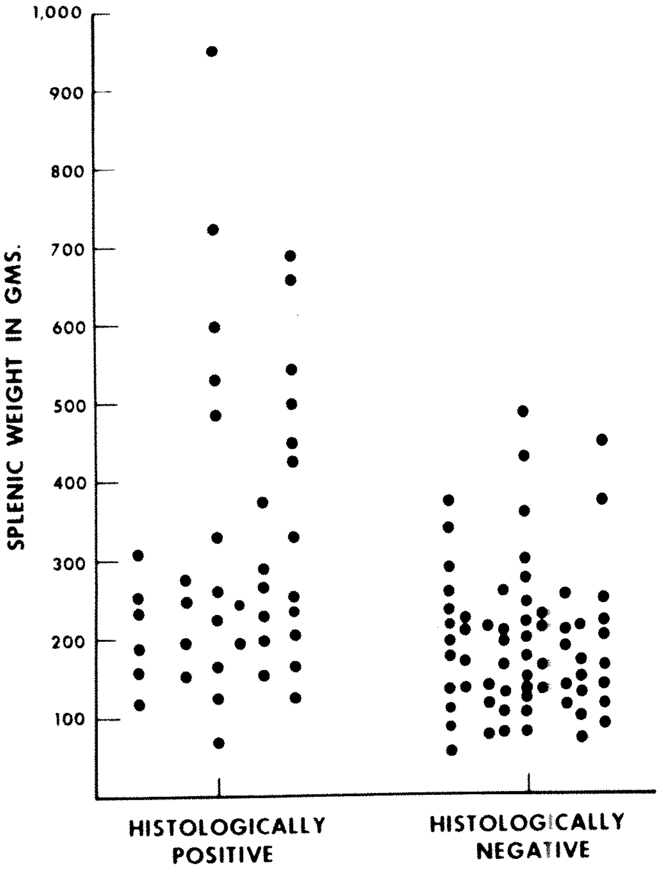


FIG. 2. The weights in grams of 41 spleens histologically positive for Hodgkin's disease compared with the weights of 65 histologically negative spleens.

not enlarged, liver function tests were normal, and the lymphangiogram was negative.

Discussion

In this series of 111 patients with Hodgkin's disease, staging laparotomy resulted in a change of stage in 36%. This figure is in essential agreement with that reported from other institutions.[4,9] The immediate clinical utility of this information is limited unless it is related to treatment. In other words, did laparotomy alter therapy and to what extent?

Retrospectively, the treatment plan that would have been used if a staging laparotomy had not been performed was compared with the treatment actually administered. In 69 of 111 patients there was no change but in the remaining 42 patients therapy was altered. Planned radiation therapy was decreased in 17 patients, increased in nine, changed to chemotherapy in six, and combined with chemotherapy in seven. In three patients planned chemotherapy was changed to radiation therapy.

These data offer convincing testimony that staging laparotomy does alter therapeutic strategy. However, potential mortality and morbidity from laparotomy must not be minimized. Although there were no deaths in the University of Virginia series, complications occurred in 12% of the patients. Kawarada et al.[5] collecting data from 719 patients who had staging laparotomy for Hodgkin's disease found that there were seven deaths (0.9%) and 73 complications (10.1%). Using questionnaires, Rosenstock et al.[8] surveyed members of the Section of Surgery of the American Academy of Pediatrics with reference to complications associated with staging laparotomy in children with Hodgkin's disease. In 347 procedures there were no operative deaths while 7.5% of the patients had complications. The largest experience from a single institution is from Stanford. In this series of 400 patients, Cannon and Nelsen[2] report no deaths; one per cent required reoperations for complications, 3.7% had major complications, and 14% minor complications.

The use of total nodal plus splenic irradiation would eliminate the need for staging laparotomy, but at the risk of overtreatment of those in whom no disease was found below the diaphragm, and inadequate treatment of those in whom stage IV disease or mesenteric node involvement was confirmed at laparotomy. Moreover, the adverse effects of radiation therapy and chemotherapy which include the risk of second malignancy, particularly acute leukemia, are not to be minimized.[1]

Conclusions

The value of exploratory laparotomy combined with liver and lymph node biopsies and splenectomy in obtaining information leading to a precise therapeutic strategy in Hodgkin's disease needs to be balanced against the potential mortality and morbidity of this operation. In the setting of currently available diagnostic and therapeutic options, a staging laparotomy will continue to be recommended for all patients with Hodgkin's disease excepting those in whom Stage IV disease is established or apparent or in whom a major diagnostic operation is considered ill-advised because of medical and other reasons.

References

1. Cadman, E. C., Capizzi, R. L. and Bertino, J. R.: Acute Nonlymphocytic Leukemia: A Delayed Complication of Hodgkin's Disease Therapy: Analysis of 109 Cases. Cancer, 40:1280, 1977.
2. Cannon, W. B. and Nelsen, T. S.: Staging of Hodgkin's Disease: A Surgical Perspective. Am. J. Surg., 132:224, Aug. 1976.
3. Carbone, P. P., Kaplan, H. S., Musshoff, K., et al.: Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res., 31:1860, 1971.

4. Glatstein, E., Guernsey, J. M., Rosenberg, S. A. and Kaplan, H. S.: The Value of Laparotomy and Splenectomy in the Staging of Hodgkin's Disease. Cancer, 24:709, 1969.
5. Kawarada, Y., Goldberg, L., Brady, L., et al.: Staging Laparotomy for Hodgkin's Disease. Am. Surg., 42:332, May 1976.
6. Lukes, R. J., Craver, L. F., Hall, T. C., et al.: Report of the Nomenclature Committee. Cancer Res. 26:1311, 1966.
7. Lukes, R. J.: Criteria for Involvement of Lymph Nodes, Bone Marrow, Spleen, and Liver in Hodgkin's Disease. Cancer Res., 31:1755, 1971.
8. Rosenstock, J. G., D'Angio, G. J. and Kiesewetter, W. B.: The Incidence of Complications Following Staging Laparotomy for Hodgkin's Disease in Children. Am. J. Roentgenol. Radium Ther. Nucl. Med., 120:531, 1974.
9. Sutcliffe, S. B. J., Wrigley, P. F. M., Smyth, J. F., et al.: Intensive Investigation in Management of Hodgkin's Disease. Br. Med. J., 2:1343, 1976.

DISCUSSION

DR. RICHARD G. MARTIN (Houston, Texas): We at the Anderson Hospital have been very active in staging patients with Hodgkin's disease, and our findings are very similar to those that have just been presented.

Of course, the main question that has not been answered is: Does staging increase life expectancy in these cases? And I don't believe we will have that answer for some time as yet. But, certainly, we do think that staging is very important.

We do not routinely stage all of ours; only those adults with negative lymphangiograms and clinical Stage I, II, and III [sic] in children over six years of age. And as has been pointed out, I feel that the surgeon has a great responsibility in choosing which patients are to be staged and which are not. And every patient sent to us must be examined to be sure that he is physically capable of undergoing such a procedure, because, as you have seen, it is not an innocuous procedure, and it is an elective surgical procedure.

Any patient that has mediastinal involvement must carefully be evaluated for adequate respiratory function and, if necessary, this area should be treated before performing a staging laparotomy.

We feel that staging laparotomy is very important, even though we do not know the answer as to life expectancy, because if you treat the abdomen with x-ray therapy, we want to make sure that there is a reason for it. And as many know, I am certainly one who does not like to see x-ray therapy given to the abdomen unless it's necessary.

One brief word may be mentioned in comparing staging of Hodgkin's disease with non-Hodgkin's lymphoma. The non-Hodgkin's lymphoma patient is usually much sicker, and the complication rate is a lot higher. However, here again it is important, because often the mesenteric nodes are positive in the non-Hodgkin's, compared to the Hodgkin's, and these do not show up on lymphangiogram.

DR. ARTHUR J. DONOVAN (Mobile, Alabama): I would like to discuss one facet of intraoperative management of the patient who has a positive lymphangiogram. In the past, at the post-celiotomy conference for decision as to therapy, I have been embarrassed to be shown on the abdominal films the same opacified lymph nodes that were supposed to have been removed, based on the positive lymphangiogram. These nodes had not been removed during the operation. The radiotherapist then adopted the position that Stage 3 disease must be assumed and the patient be treated with total nodal radiation.

Several years ago, I adopted a policy that a scout film of the abdomen be obtained before closing the abdomen. On three occasions I have found that the specific lymph nodes that I was supposed to remove were still within the abdominal cavity. In two of these instances, the lymph nodes were posterior to the right renal vein; in one of these cases the lymph nodes were positive.

I would recommend this procedure and ask the group from Charlottesville if, when there is positive lymphangiogram, they obtain an abdominal scout film on the operating table and prior to the closing of the abdominal wall. To reiterate, the purpose is to assure that the suspicious lymph nodes have been removed.

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): I would like to ask Dr. Sandusky if he would comment on his feeling about the splenectomy involved in the staging laparotomy for patients with Hodgkin's disease.

He and his associates over the years have helped us a great deal in understanding the problem of postsplenectomy infections, and one of the major complications in children and young adults with Hodgkin's disease who have had splenectomy has been the problem of overwhelming sepsis following splenectomy.

I would like to ask him how he feels currently about *excluding* splenectomy. I know he commented upon the difficulty in deciding by inspection which spleens were involved with Hodgkin's. Would he consider doing hemisplenectomies, or partial splenectomies? What is his current feeling about the necessity for removing the spleen in patients with Hodgkin's disease?

DR. J. SHELTON HORSLEY, III (Closing discussion): I would certainly agree with what Dr. Martin said, that we would like to avoid irradiation of the lymph nodes in the abdomen if at all possible. I think it's tremendously important that the surgeon, the medical oncologist, hematologist, and radiation therapist talk to one another. It's of primary importance, particularly in this disease. This should be a multidisciplinary approach. The surgeon is really a technician in Hodgkin's Disease. This is a diagnostic procedure. We should not be doing staging laparotomies unless our results will affect the ultimate treatment of the patient.

Dr. Donovan, bless your heart! This is one point that we wished to stress. You must take an intraoperative x-ray of the patient before you close the abdomen, if you are going to get the suspicious nodes seen on the preoperative lymphangiogram.

Dr. Tegtmeyer, who does the lymphangiograms at the University of Virginia, and did the vast majority of these, was one of us. He's a surgeon who, as he said, "saw the light and went into radiology." It's a real pleasure to work with him because he gives you a definitive diagnosis. We review these films preoperatively with him. If he outlines a suspicious node, at the time of surgery we remove this node, mark the area with metallic clips, get a radiograph, and if that node is still there, we pursue it until it's removed, and again confirmed by an intraoperative x-ray.

Dr. Haller's question is a very pertinent one. We have had very little experience with staging Hodgkin's disease in children. The few that we have done have been otherwise quite healthy. We have removed the spleens and placed them on long-term prophylactic antibiotics.

In the adults, we have had no patients in whom we could attribute any significant or serious infection to splenectomy. As Dr. Sandusky has shown on one of his slides, we were unable to correlate size with involvement of the spleen. We feel, therefore, that we must do a splenectomy and give the entire spleen to the pathologist for definitive histologic study.

I would like to emphasize again that this is a diagnostic test. As other diagnostic tests become more accurate, we will do fewer staging laparotomies in Hodgkin's disease. I refer particularly to bone marrow biopsies, lymphangiography and laparoscopy with direct needle biopsies of the liver.

Breast Reconstruction Following Mastectomy for Cancer

JOHN B. LYNCH, M.D., JAMES J. MADDEN, JR., M.D., JOHN D. FRANKLIN, M.D.

From the Department of Plastic Surgery,
Vanderbilt University Medical Center,
Nashville, Tennessee

Breast reconstruction following mastectomy for cancer is a feasible procedure. The selection of the proper type of mastectomy should be the decision of the cancer surgeon. However, with the advent of modified mastectomies, the use of fewer primary skin grafts, and the preservation of all or part of the pectoralis major muscle, breast reconstruction has become more satisfactory. Since many women adjust poorly to mastectomy, the chance for reconstruction offers hope for a fuller life. Reconstruction of the postmastectomy cancer patient can be accomplished in three basic steps: 1) An adequate breast mound can be constructed with a prosthesis. A flap may be used if the skin cover is inadequate. 2) The size and shape of the remaining breast can be adjusted to obtain symmetry. 3) The nipple-areola complex can be reconstructed if the patient desires. Correction of the infraclavicular and axillary defects may be required. The techniques employed in 14 patients are presented.

About 70,000 new cases of breast cancer are detected annually in the United States. Of newborn girls, one in 15 is destined to develop carcinoma of the breast sometime in her life.[28] Since the development of mammography, detection clinics, and public information about self examination, many of these cancers are being detected sooner. There is a current trend for surgeons to select a modified radical mastectomy, and with the development of the silicone mammary prosthesis, reconstruction after mastectomy is now more satisfactory and feasible. Consequently, more patients are seeking breast reconstruction.

Snyderman[27] has estimated that approximately 80% of the women undergoing mastectomies will adjust well to external prostheses. However, there is a wide variation in the degree of adjustment. Nearly all postmastectomy patients undergo transient depression.[24] In the past, reconstructive efforts have frequently been cumbersome, requiring multiple operations over extended periods and producing a less than satisfactory result.[2,7,13,16,18,30]

The first surgical awareness of the necessity of preserving or reconstructing cosmetically acceptable breasts was evidenced about 1669.[22] Durstan reported the first attempt at breast reconstruction, in which he tried to correct ptotic breasts. The classical Halsted radical mastectomy was introduced in 1894; and surgeons have tried various methods of reconstructing the breast since that time. Much of the early work, performed by German surgeons, was extensive, deforming, and unsatisfactory. A variety of reconstructive methods have been advocated such as free fat and dermal grafts. In general, breast reconstruction in the past followed, basically, two variations of tube pedicle flaps. One source of tube pedicle tissue was the opposite breast. Thorek[31] in 1942 described a complicated multistage procedure credited to Wilhelm Rinhardt; and, Harris,[13] in 1949; and Holdsworth,[16] in 1956, described techniques of employing the opposite breast. The use of tube pedicle tissue developed as a thoracoabdominal flap was introduced in 1952 by Sir Harold Gillies.[7] This technique also required multiple stages.

Reconstruction of the breast remained a staged tube pedicle procedure until the 1960's. In 1964, Cronin and Gerow[5] first described a subcutaneous prosthesis consisting of a gel form of dimethylpolysiloxane in a silicone envelope. This prosthesis, and variations of it, has gained world wide approval by plastic surgeons and has simplified the reconstruction of the postmastectomy breast. In 1974, Tai and Haseqawa[30] used a transverse abdominal flap based medially in the thorico-epigastric area to reconstruct the chest wall. This is an axial arterialized flap and can be raised primarily for immediate breast reconstruction. In 1976, Jurkiewicz et al.[3] demonstrated a good result with one stage reconstruction of the breast mound using an omental flap over a prosthesis with immediate skin grafting.

In recent years, immediate resurfacing with local arterial flaps when skin cover is inadequate and silicone prostheses have made possible a better and more expedient reconstruction.[6,8–10,12,14,15,18,29] This report will present 14 patients who have undergone breast

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

0003-4932-78-0500-0490-0115 © J. B. Lippincott Company

reconstruction after mastectomy at Vanderbilt University Hospital over the past three years.

Clinical Data

A total of 14 patients have been selected for reconstruction following mastectomy for carcinoma at Vanderbilt University Hospital. Their age at time of diagnosis ranges from 20 to 52. The timing of reconstruction has ranged from four months to 26 years postmastectomy. Eight patients had standard radical mastectomies, one patient had bilateral simple mastectomy, four patients had modified radical mastectomies, and one patient had bilateral radical mastectomy. Four of the patients who underwent radical mastectomy had postoperative radiotherapy.

The pathology of these tumors, by and large, was infiltrating ductal carcinoma. Nine patients had negative nodes; and 4 patients had positive nodes. Two of these had only one positive node in the axilla. One patient had a noninvasive intraductal carcinoma and underwent simple mastectomy. The review of sections from another patient who had a radical mastectomy revealed a papillary cystadenoma, rather than carcinoma (Table 1).

Case Reports

Case 1. M. DeP. was 52-years-old when right radical mastectomy was performed. She had no carcinoma identified in her breast but had a positive axillary node. Twenty-seven months postoperatively the first stage of reconstruction consisting of placement of a 210 cc gel prosthesis beneath the skin of her right chest was initiated. At the same time a medially based thorico-epigastric flap was used to replace an ischemic area of skin identified with i.v.

TABLE 1. *Summary of 14 Patients Reconstructed.*

Name	Age Dx	Treatment	Pathology	Timing of Reconst.	Reconst. Procedure
1. M.DeP.	52	Radical, right	1 + ax node	27 mo.	2*
2. S.G.	20	Radical, left reconstruction-7 mo.	Papillary cystadenoma	14 years	3
3. G.H.	46	Radical, right reconstruction-9 mo.	Neg nodes	8 years	3
4. B.J.	28	Radical, left reconstruction-9 mo.	Neg nodes	3½ years	3
5. S.J.	27	Radical, right post-op radiotherapy reconstruction-27 mo.	Neg nodes	3 years	3
6. V.L.	40	Radical, left post-op radiotherapy	+ nodes	9 years	2*
7. H.O.	40	Radical, right post-op radiotherapy failure (moved)	Neg nodes	2 years	5
8. B.W.	50	Radical, right post-op radiotherapy	1 + node	9 mo.	2*
9. Z.W.	44	Radical, right post-op radiotherapy 7 years later radical, left reconstruction-14 mo.	+ nodes, right Neg nodes, left	13 years	4
10. H.G.	20	Bil. simple mastectomies	Intraductal ca, left fibrocystic disease, right	26 years	1
11. S.B.	31	Modified, left	Neg nodes	15 mo	2*
12. M.C.	29	Modified, right reconstruction-31 mo	Neg nodes	6 mo	5
13. C.F.	26	Modified, left reconstruction-8 mo	Neg nodes	4 mo	3
14. M.G.	34	Modified, left incomplete (moved)	Neg nodes	7 mo	2

* Further procedures planned.

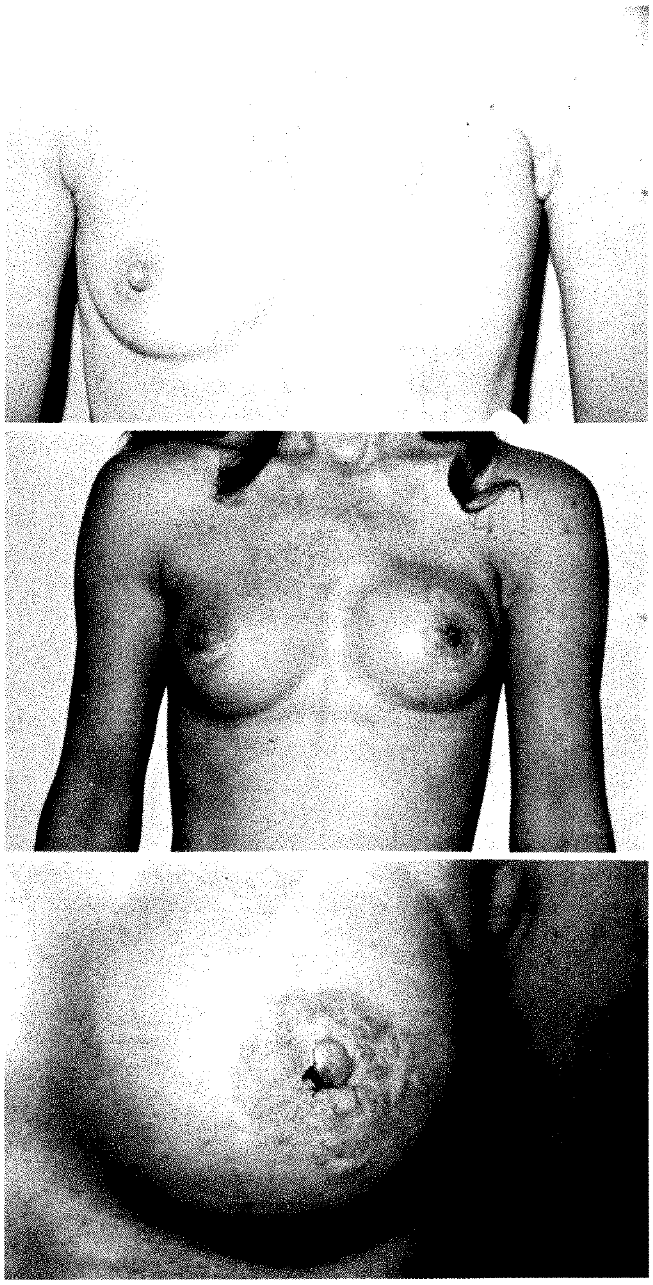


FIG. 1. (a, top) Case #2: Prereconstruction appearance. (b, center) Case #2: Post-reconstruction appearance. (c, bottom) Case #2: Reconstructed nipple-areola.

fluorscein. The pocket was also enlarged. Thirteen months later a mastopexy was performed on the left breast and a 400 cc gel prosthesis was placed on the right. She is now awaiting nipple reconstruction.

Case 2. S.G. was 20-years-old when she underwent a left radical mastectomy. She was thought to have carcinoma but, on review of her sections, the tumor was determined to be a papillary cysadenoma. Fourteen years later, reconstruction was begun with a 200 cc prosthesis on the left. Her right breast was augmented with a 100 cc prosthesis. Two months, later, the left nipple was reconstructed. Her reconstruction was completed 17 months after it began with placement of a 130 cc saline-filled prosthesis on the right (Fig. 1).

Case 3. G.H. was 46-years-old when her right radical mastectomy was performed. Her axillary nodes contained no tumor. Eight years later, her reconstruction was begun by placing a 180 cc gel prosthesis under the skin of the right chest. Five months later, she underwent mastopexy on the left and a 280 cc implant was placed on the right. Four months later, the right implant was increased to 400 cc. The left breast was augmented with a 165 cc gel implant. Her right nipple-areola complex was reconstructed utilizing split grafts from the opposite areola and full thickness grafts from the nipple.

Case 4. B.J. was 28-years-old when she had a left radical mastectomy. She had no positive nodes. Three and one half years later, breast reconstruction was initiated by placing a 240 cc implant under the skin of the left chest. Two months later, a right mastopexy was performed. Eight months after that, a latissimus dorsi muscle flap was used to correct the infraclavicular defect. A larger prosthesis was also placed on the left. Left nipple reconstruction was accomplished utilizing the nipple-areola complex from the opposite breast.

Case 5. S.J. underwent a right radical mastectomy at age 27. She had no positive nodes but received postoperative radiotherapy. Her reconstruction was begun three years later with a mastopexy on the left. One year later, a 220 cc gel implant was placed on the right side and dermal fat graft was placed in the lateral pectoral area. One and one half years later, the implant on the right was increased to 280 cc gel and nipple reconstruction was performed. Total time for reconstruction was 27 months.

Case 6. V.L. was 40-years-old when she underwent left radical mastectomy. She had positive nodes in the axilla and received postoperative radiotherapy. Nine years later, her reconstruction began with the placement of a 325 cc saline implant under the skin in the left chest. Four months later, a mastopexy was performed on the right, and a 400 cc gel implant was placed on the left. The patient is now awaiting nipple reconstruction.

Case 7. H.O. was 40-years-old when she had a right radical mastectomy. She had no positive nodes in the axilla but received postoperative radiotherapy. Her reconstruction was begun 24 months after mastectomy. Initially it consisted of a laterally based chest rotation flap to increase the amount of skin and soft tissue in the area of the scar. A large infraclavicular defect, due to the removal of the pectoralis major muscle, was originally corrected with a custom-made gel implant. The implant subsequently developed a capsule which was deforming and had to be removed. A total of five different procedures were performed over a 17 month period. Wound complications and infection resulted in extrusion of the implant. She has subsequently moved away and has been lost to follow-up.

Case 8. B.W. was 50-years-old when she underwent right radical mastectomy. One of 13 nodes was positive, and she received postoperative radiotherapy. Her reconstruction began 9 months later with the placement of a 300 cc saline implant on the right. Three months later, a mastopexy was performed on the left and the prosthesis on the right was increased. A latissimus dorsi muscle flap was used to fill the defect in her right infraclavicular area.

Case 9. Z.W. has had bilateral radical mastectomies. The first mastectomy was performed at age 44. At that time she had positive nodes and received postoperative radiotherapy. the next mastectomy was performed when she was 51-years-old. Thirteen years after the original carcinoma was removed, her reconstruction began. Since she has complete heart block and a cardiac pacemaker in place, all her procedures, except the last, were performed under local anesthesia. The first procedure consisted of placing 220 cc gels on either side. Four months later, nipples were reconstructed by utilizing the labia and the infraclavicular defects were corrected by creating anterior axillary folds using a buried dermal fat technique. Reconstruction was essentially completed in four months. Subsequently, the scars in the anterior axillary area have been revised. Fourteen months after reconstruction was initiated, her implants were increased with 300 cc gels bilaterally.

Case 10. H.G. was 20-years-old when a noninvasive intraductal carcinoma of her left breast was diagnosed. She also had fibrocystic disease on the right. Bilateral simple mastectomies were performed. Twenty-six years later, she sought reconstruction. 210 cc gel implants were placed on either side. She has been quite satisfied with the partial reconstruction and desires no further surgery.

Case 11. S.B. underwent modified mastectomy for infiltrating intraductal carcinoma at age 31. She had no positive axillary nodes. Fifteen months later, a 210 cc gel prosthesis was placed on the left side. Seven months later she had a mastopexy combined with an augmentation of the right breast with a 150 cc gel prosthesis. The prosthesis on the left was increased to 250 cc.

Case 12. M.C., at age 29, underwent a modified radical mastectomy with an attempt at immediate reconstruction. She had Paget's disease of her right breast and no axillary nodes were positive for tumor. Reconstruction was completed over a period of 31 months with five procedures. Reconstruction consisted of gradually increasing the prosthesis in her right chest area until a 400 cc gel prosthesis was in place. On the left, a mastopexy combined with augmentation with a 150 cc prosthesis was performed. The right nipple was reconstructed with a split graft from the left nipple-areola complex.

Case 13. C.F. underwent a modified radical mastectomy at age 26 for an infiltrating ductal carcinoma. She had no positive nodes. Four months after her operation, a 175 cc inflatable prosthesis was placed on the left. Three months later, under local anesthesia, this volume was increased to 250 cc. Her reconstruction was completed with a right mastopexy and nipple reconstruction 12 months following mastectomy.

Case 14. M.G. underwent a modified left radical mastectomy at age 34. She had a colloid carcinoma with no positive nodes. Seven months after her mastectomy, a 200 cc saline inflatable prosthesis was placed on the left. Four months later this volume was increased to 450 cc with a gel prosthesis. The right breast was reduced.

Discussion

At present not all cancer surgeons agree on what constitutes an adequate procedure for cancer of the breast. Currently, an increasing number of patients are being seen who have had modified mastectomy. Fewer patients have primary skin grafts; and preservation of part, or all, of the pectoralis major muscle is more commonly seen. Although the reconstructive surgeon does not, and should not determine what constitutes an adequate surgical procedure for an individual patient, the more frequent utilization of lesser procedures with preservation of the pectoralis major makes satisfactory reconstruction easier to accomplish.[32]

Indications–Contraindications

Reconstruction of any well motivated patient should be seriously considered if the patient's surgeon feels reasonably sure that the disease has been eradicated locally. These patients are usually those with small, early, stage one lesions. The presence of positive axillary nodes, or the use of postoperative radiotherapy is not necessarily a contraindication. Although properly administered, postoperative use of x-ray therapy can increase the incidence of local complications. Advanced x-ray changes in the skin may necessitate resurfacing with an arterialized flap. Reconstruction is usually contraindicated in inflammatory carcinoma, or in large aggressive lesions with questionable local eradication and/or extensive axillary involvement. Subjecting a patient to a multistage reconstruction, when there is a good possibility of local or systemic recurrence is usually not justified.

Psychological Aspects

Almost any woman, especially a young one, who is faced with the prospect of a radical mastectomy fears not only death but the mutilation of her body. The prospect of possible reconstruction of the breast can provide great consolation even before the operation. It is probable that if a woman knows the possibility of breast reconstruction, she may seek consultation sooner when the carcinoma has a better prognosis.

Renneker and Cutler[24] have reported a psychological study of women who have undergone breast amputation. Depression seems to be a common sequela to mastectomy and is marked by anxiety, insomnia, depressive attitudes, occasional ideas of suicide and a feeling of shame and worthlessness. Women seem to mourn the loss of their breasts, and to equate removal with the loss of their badge of femininity. Psychologically, it has the same qualitative meaning as the loss of the penis in the male.

There is also an unshakeable, and universally unconscious, symbolic connection between the breast and motherhood. The breast is a symbol of a woman's pride in her sexuality and in her motherliness. To threaten the breast is to shake the very core of her feminine orientation. One of John Hueston's patients succinctly summarized her feelings toward mastectomy and reconstruction when she stated that "the mastectomy saved my life—the reconstruction has made it worth living."[17]

Timing

To delay reconstruction until reasonable assurance of cure is present would require a minimum of several years. Half of those patients not cured following surgery live at least two and one half years while 25% will survive five years or more.[25] Early reconstruction gives the woman a psychological boost at the time when it is needed the most. One would not wish to subject a poor-risk patient to multiple operative procedures. If the prognosis is favorable, however, there

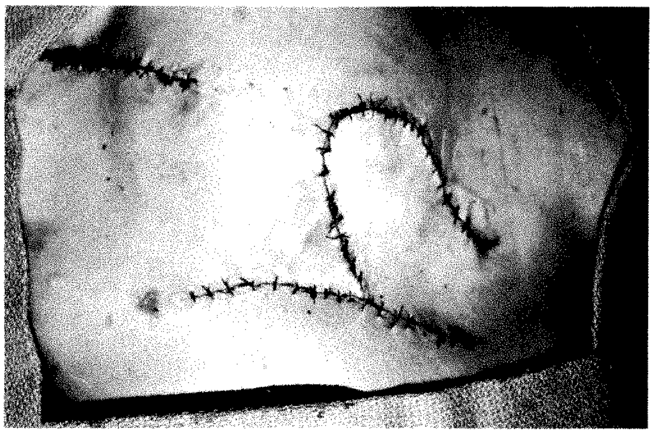


FIG. 2. Case #1: Initial reconstruction. Two hundred-ten cc gel placed beneath skin. Flap used to replace area of ischemic skin identified with intraoperative fluorscein.

appears to be no advantage in delaying reconstruction for an arbitrary period of time. Reconstruction should be initiated as soon as the wounds are well-healed and the skin is reasonably soft. For several years Hueston[18] has advocated that at the completion of surgery, the wound should be simply dressed and not closed. This permits the pathologist to evaluate the specimen and helps insure good viability of the skin flaps. If everything appears to be satisfactory on the fourth to fifth postoperative day, Hueston has inserted implants so that the patient goes home from the hospital with the breast mound re-established. In the Vanderbilt series of patients, reconstruction was instituted from four months to 26 years postmastectomy. Therapy was most often initiated when a patient sought reconstruction, not when the authors would have preferred.

Goals of Reconstructive Surgery

Although many patients are satisfied with the initial reconstruction of a suitable breast mound, the ideal reconstructive goals may include any, or all, of the following: 1) Resurfacing to provide adequate skin cover, using locally arterialized flap such as the medially based inframammary flap described by Cronin.[6] 2) Creation of a satisfactory breast mound, often using a small initial implant which is replaced after appropriate stretching of the skin and formation of a capsule. 3) Reduction, augmentation, correction of ptosis, or other modification of the remaining breast. 4) Correction of the infraclavicular and axillary defect. 5) Reconstruction of the nipple-areola complex.

Usually the soft tissue is adequate for insertion of a subcutaneous prosthesis. When there is a deficiency of soft tissue, the use of a medially based thoraco-epigastric flap may be combined with the insertion of a prosthesis as the initial procedure. The routine intraoperative use of fluorscein to evaluate the viability of skin flaps is an essential part of the initial reconstructive procedure (Fig. 2).[26]

If, at the initial procedure, the skin will not accomodate the size implant desired, a larger one may be inserted later. After a fibrous capsule has formed around the initial implant, subsequent enlargement of the pocket and replacement with a larger prosthesis can be performed with a minimal chance of extrusion of the prosthesis.

Once the reconstructed mound has been developed to the desired size, it is usually necessary to effect some adjustment of the remaining breast. The remaining breast is frequently ptotic and larger than the reconstructed mound. Invasion of the remaining breast should not be undertaken lightly since breast cancer is frequently a bilateral disease. Surgeons should probably consider extirpation of the remaining breast more seriously than they do at the present time. At any rate, the correction of ptosis or partial reduction of the remaining breast does not appear to interfere with follow-up manual or x-ray examination.[27]. In order to obtain a satisfactory reconstruction, it is essential that the breasts be reasonably symmetric.

The classical radical mastectomy leaves the patient with an infraclavicular depression and loss of the anterior axillary fold. These deformities prevent her from wearing sleeveless or low-necked clothing. The axillary and infraclavicular defects may be corrected in a variety of ways. Custom-made silicone implants for contouring of the infraclavicular defect are available and, for many patients, are quite satisfactory. However, these often develop a firm, fibrous capsule producing a pillow effect with sharply demarcated borders (Fig. 3). The use of de-epithelialized dermal flaps, reattached to the clavicle, can be helpful in overcoming this defect but additional scars sometime result which are

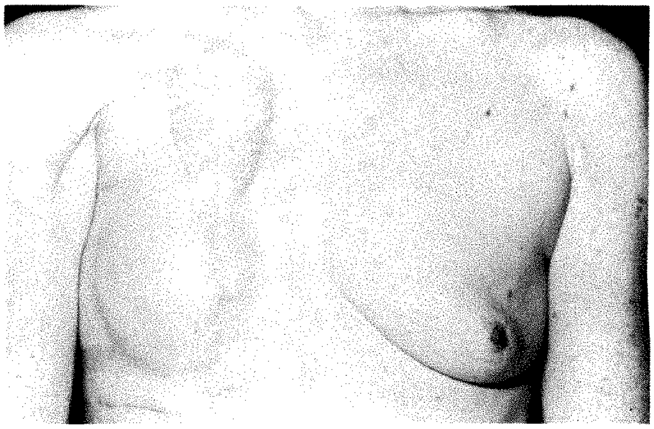


FIG. 3. Case #7: Pillow effect produced by custom made infraclavicular prosthesis due to capsule formation and contracture.

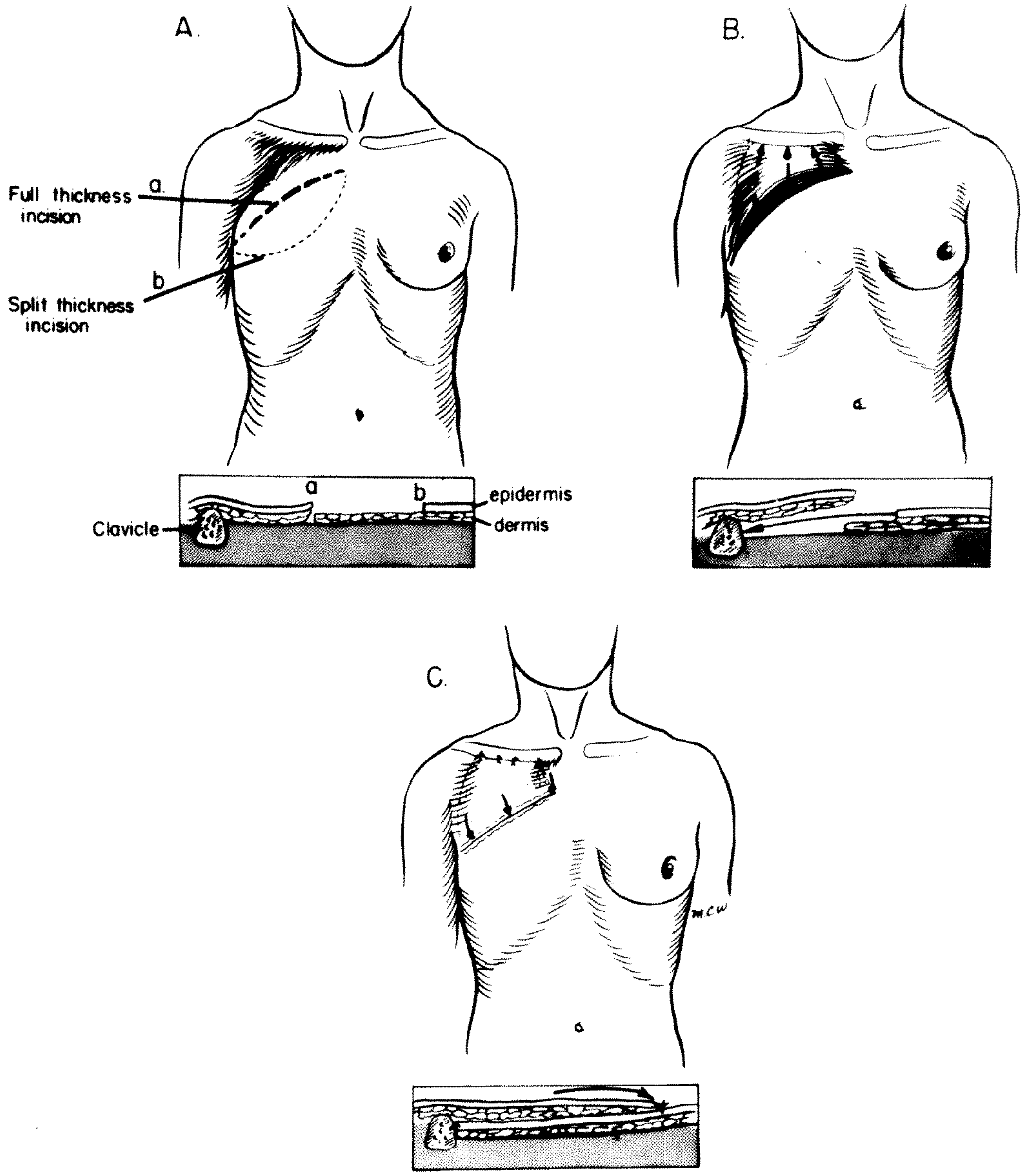


FIG. 4. (A–C) Dermal flap technique used to correct anterior axillary and infraclavicular defects.

objectionable to the patient (Fig. 4). The use of the anterior portion of the latissimus dorsi muscle serves to minimize the infraclavicular defect and effaces the prominent posterior axillary fold (Fig. 5). The use of a custom-made implant covered by the latissimus dorsi flap may be more satisfactory in minimizing this deformity. Many patients prefer no further reconstruction if an adequate mound and adjustment of the remaining breast establish reasonable symmetry and a satisfactory appearance in clothing. However, some patients desire a nipple-areola reconstruction. Banking the nipple and areola as a free graft in the abdomen or inguinal area at the time of initial mastectomy has been advocated for use in subsequent reconstruction.[14,20] This is, obviously, a controversial procedure because of the theoretical possibility of transferring cancer cells. In patients who have undergone bilateral mastectomy, reasonable areola simulation can be accomplished by the use of free full thickness labial grafts which provide a circle of granular pigmented skin[1,34] (Fig. 6). The insertion of a small button of conchal cartilage in a subsequent procedure provides some projection in the center to simulate a nipple.[4,7] In unilateral mastectomy, when one normal nipple remains, the use of the labial graft generally provides a poor color match and unsatisfactory nipple-areola reconstruction. Many techniques, such as tattooing, have been advocated, but the results are generally inferior.[10,23] Currently, the best techniques for unilateral nipple-areola reconstruction involve utilizing a portion of the remaining nipple in

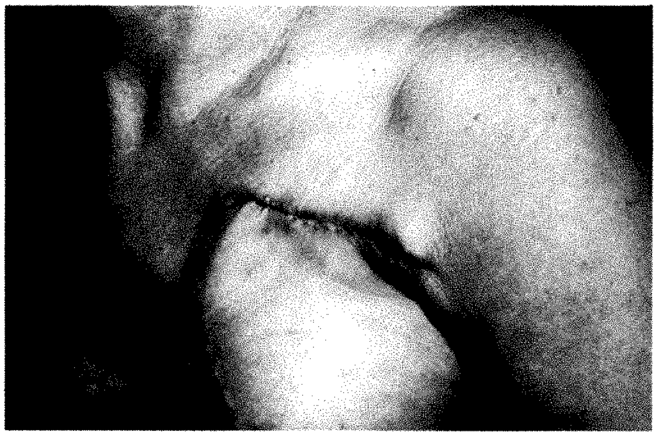


FIG. 4D. Case #9: Correction of infraclavicular defect with dermal flap showing early appearance of scar.

some way. This can be accomplished as a split thickness skin graft of the areola and a full thickness graft of the nipple from the remaining normal breast.[11,21] A variety of techniques designed to "halve" the remaining nipple have been described.[6,32] The use of a split thickness areola and full thickness nipple graft provides an optimum nipple-areola reconstruction (Fig. 7). This may result in some de-pigmentation and color changes of the donor site (Fig. 8). The halving technique is quite suitable if the remaining nipple is large but can result in inadequate nipple size when the donor area is small.

Program for Reconstruction

As our experience with breast reconstruction has increased, a more standardized program has evolved as

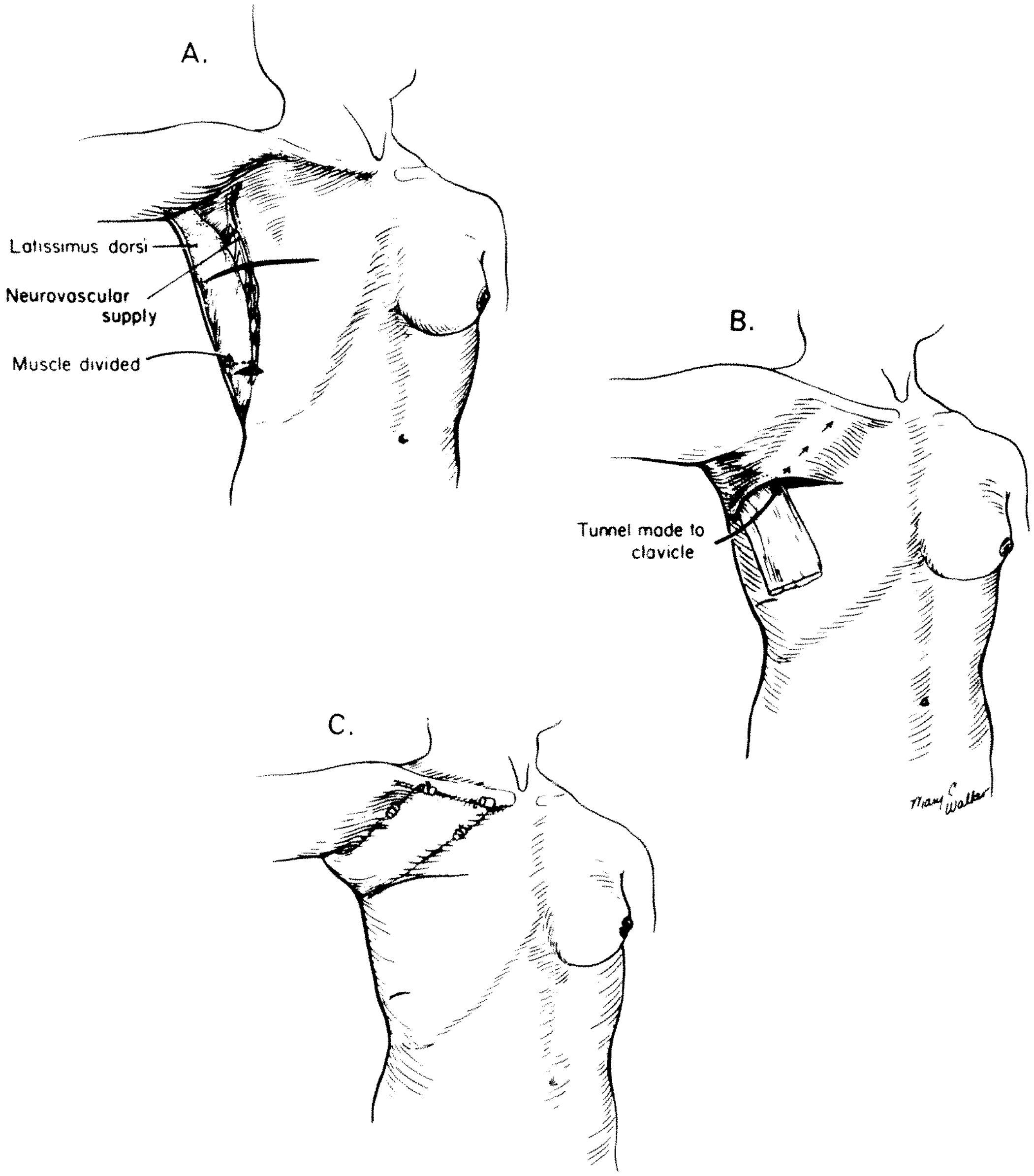


FIG. 5. Diagrams illustrating use of latissimus dorsi flap.

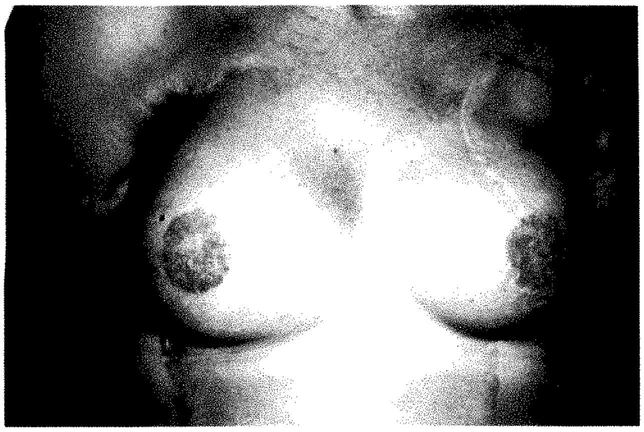


FIG. 6. Case #9: Post-reconstruction demonstrates areolae reconstruction utilizing labial grafts. Same patient who had dermal flaps bilaterally.

follows: 1) Initial insertion of as large an implant as the skin will tolerate. If there is inadequate skin cover, resurfacing with medially based inframammary flap is required. 2) After about three months, if healing has been uncomplicated, the reconstructed side is enlarged to the desired size. Symmetry is accomplished by reduction, augmentation, and/or correction of ptosis of the remaining breast. 3) After an additional 3 months, the infraclavicular or axillary defect may be corrected if desired. The nipple-areola complex may be reconstructed at either step 2 or 3.

These 3 basic steps of reconstruction may be accomplished in 6 months. Obviously, in many patients, some additional minor touch-ups or additional steps may be required. Infection or other complications may necessitate additional surgical procedures. The program outlined is a definite improvement over procedures advocating migration of tube pedicle flaps which require multiple stages over a period of many months.

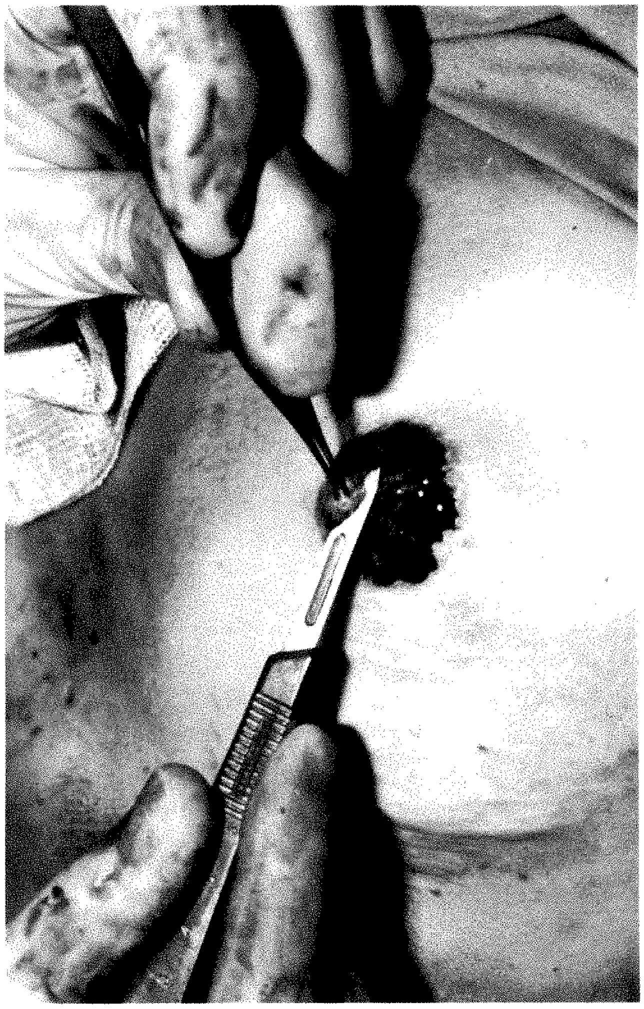


FIG. 7b. Case #5: Taking composite graft from nipple.

Other innovative methods of reconstruction have been introduced. For example, Jurkiewicz et al.[3] demonstrated the creation of a breast mound using an omental flap over a custom-made prosthesis with immediate

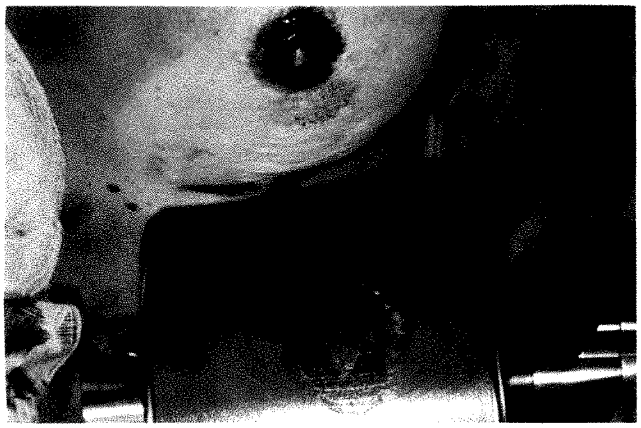


FIG. 7a. Case #5: Split skin graft from remaining nipple-areola complex to reconstruct opposite areola.

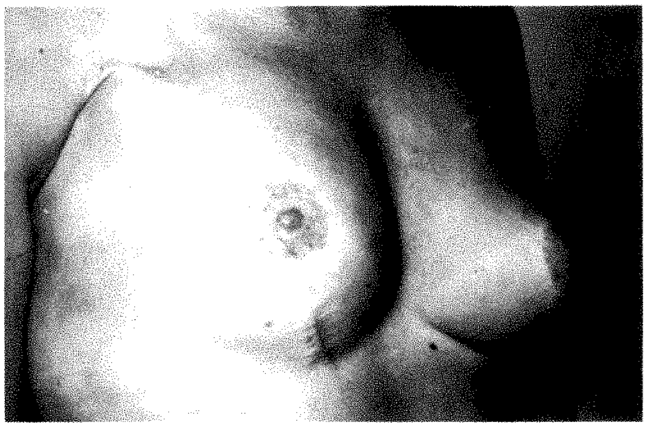


FIG. 7c. Case #5: Appearance of reconstructed nipple. She had dermal pedicle in right axilla.

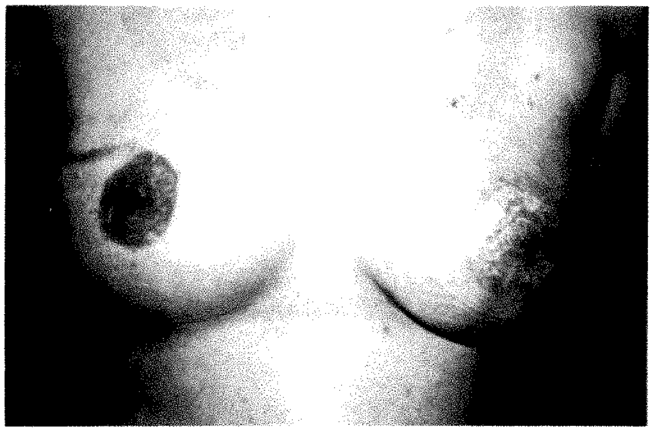


FIG. 8. Case #12: Postreconstruction demonstrating depigmentation of donor nipple-areola.

skin grafting. Because of the morbidity associated with laparotomy, the Vanderbilt schedule seems to be more conservative.

Role of the Cancer Surgeon

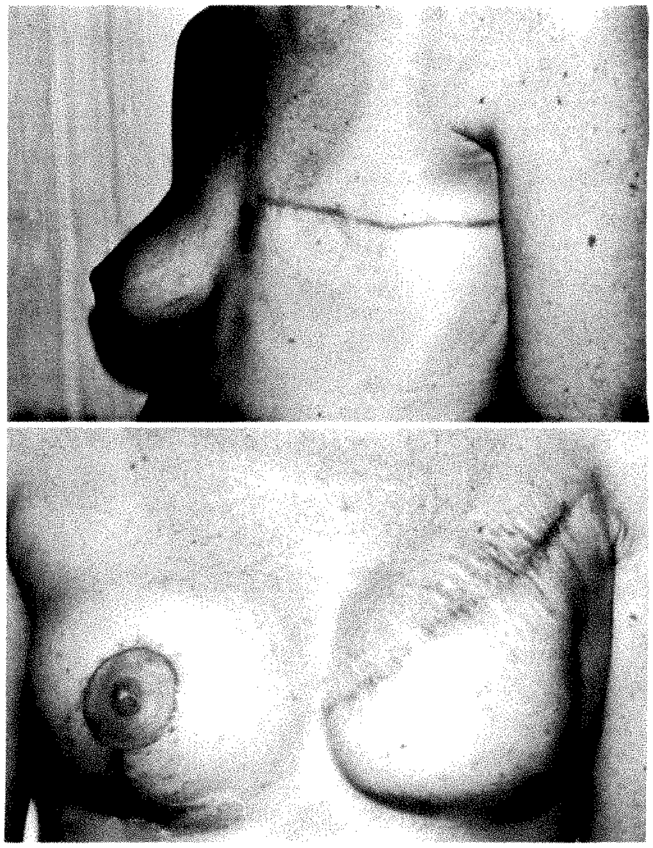
The cancer surgeon is obliged to manage his patient as his conscience dictates. However, if a patient is to be a candidate for subsequent reconstruction, the following suggestions should be considered 1) Use a transverse incision as opposed to a vertical incision (Fig. 9). 2) Avoid unnecessary excessive skin excision. 3) Perform a meticulous closure to minimize railroad track scars. 4) Preserve 3/4 to one inch of the clavicular head as a space filler if the pectoralis major muscle is to be sacrificed. 5) Evaluate if preserving the nipple-areola complex, as a full thickness graft would compromise the patient's chance for a cure. 6) Evaluate if a simple mastectomy on the opposite side might be justified.

Summary

In the treatment of carcinoma of the breast, the first consideration should be eradication of the disease. However, a woman may suffer severe psychological trauma when a breast is removed.

Women who have undergone mastectomy, especially for carcinoma which does not involve the axillary nodes, should be informed of the possibility of having the breast reconstructed. Ideally, this information should be given the patient prior to removal of the breast, *i.e.* on the night before she is to have a breast biopsy. Even the patient with more advanced disease, *i.e.* those with positive axillary nodes and the ones requiring postoperative radiotherapy, should be considered for reconstruction, especially if reconstruction is very important to her psychologically.

Breast reconstruction can usually be accomplished in three stages with minimal hospitalization and morbidity for the patient. Avoiding unnecessary skin excision, the use of a transverse incision and the performance of meticulous skin closure facilitates the reconstructive procedures. Preservation of the pectoralis major muscle, especially the clavicular head, enhances reconstruction. In most patients, with the use of the techniques described, breast reconstruction can be accomplished easily over a six month period.



FIGS. 9a and b. (a, top) Case #13: Transverse scar following modified radical mastectomy. (b, bottom) Case #4: Patient unable to wear low neck clothing due to railroad track oblique scar following classical radical mastectomy.

References

1. Adams, W. M.: Labial Transplant for Reconstruction of Loss of the Nipple. Plast Reconstr. Surg., 4:295, 1949.
2. Alexander, J. E. and Block, L. I.: Breast Reconstruction Following Radical Mastectomy Plast. Reconstr. Surg., 40:175, 1967.
3. Arnold, P. G., Hartrampf, C. R. and Jurkiewicz, M. J.: One-Stage Reconstruction of the Breast, Using the Transposed Greater Omentum. Plast. Reconstr. Surg., 57:520, 1976.
4. Brent, B. and Bostwick, J.: Nipple-Areola Reconstruction with Auricular Tissues. Plast. Reconstr. Surg., 60:353, 1977.
5. Cronin, T. D. and Gerow, F.: Augmentation mammoplasty; a new "natural feel" prosthesis. *In* Transactions Third International Congress Plastic Surgery. Amsterdam, Excerpta Medica, 1964, pp. 41–49.

6. Cronin, T. D., Upton, J. and McDonough, J. M.: Reconstruction of the Breast after Mastectomy. Plast. Reconstr. Surg., 59:1, 1977.
7. Edgerton, M. T.: Breast Reconstruction after Radical Mastectomy for Cancer. Southern Med. J., 60:719, 1967.
8. Georgiade, N. G.: Reconstruction of the breasts following mastectomy. *In* Reconstructive Breast Surgery. Saint Louis, Mosby 1976, pp. 292–317.
9. Gibson, E. W.: Reconstruction of the Breast after Mastectomy for Cancer. Clin. Plast. Surg., 3:371, 1976.
10. Gruber, R. P.: Method to Produce Better Areolae and Nipples on Reconstructed Breasts. Plast. Reconstr. Surg., 60:505, 1977.
11. Guida, C. A., Picchi, A. and Inzirillo, S.: Areola and Nipple Reconstruction. Plast. Reconstr. Surg., 56:454, 1975.
12. Guthrie, R. H.: Breast Reconstruction after Radical Mastectomy. Plast. Reconstr. Surg., 57:14, 1976.
13. Harris, H. R.: Automammaplasty. J. Internat. Coll. Surg., 12: 827, 1949.
14. Hartwell, S. W., Anderson, R., Hall, M. D. and Esselstyn, C: Reconstruction of the Breast after Mastectomy for Cancer. Plast. Reconstr. Surg., 57:152, 1976.
15. Hauschild, W. A.: Reconstruction of the Female Breast After Bilateral Simple Mastectomy. Brit. J. Plast. Surg., 23:54, 1970.
16. Holdsworth, W. G.: A Method of Reconstructing the Breast. Brit. J. Plast. Surg., 9:161, 1956.
17. Hueston, J. T.: Surgical Correction of Breast Asymmetry. Aust. N.Z.J. Surg., 38:112, 1968.
18. Hueston, J. and McKenzie, G.: Breast Reconstruction after Radical Mastectomy. Aust. N.Z.J. Surg., 39:367, 1970.
19. Millard, D. R.: Breast Reconstruction after a Radical Mastectomy. Plast. Reconstr. Surg., 58:283, 1976.
20. Millard, D. R., Devine, J. and Warren, W. D.: A Plea for Saving the Uninvolved Nipple. Am. J. Surg., 122:763, 1971.
21. Millard, D. R.: Nipple and Areola Reconstruction by Split-Skin Graft from the Normal Side. Plast. Reconstr. Surg., 50:350, 1972.
22. Rees, T. D.: Plastic surgery of the breast: *In* Reconstructive Plastic Surgery. Philadelphia Saunders Company; 1977, pp. 3661–3663.
23. Rees, T. D.: Reconstruction of the Breast Areola by Intradermal Tattooing and Transfer. Plast. Reconstr. Surg., 55:620, 1975.
24. Renneker, R. and Cutler, M.: Psychological Problems of Adjustment to Cancer of the Breast. JAMA, 148:833, 1952.
25. Rush, B. F.: The Mathematics of Therapy in Cancer of the Breast. Presented at the 71st Annual Meeting of the Southern Medical Association. Dallas, Texas; Nov. 7, 1977.
26. Singer, R., Lewis, C., Franklin, J. and Lynch, J. B.: Intravenous Fluorscein—An Aid in the Prediction of Breast Flap Viability During Reconstruction. Presented at the Meeting of the American Society for Aesthetic Plastic Surgery, Inc., Los Angeles, California, March 23, 1977.
27. Snyderman, R. K.: Editorial—On Breast Reconstruction after Mastectomy for Cancer. Plast. Reconstr. Surg., 57:224, 1976.
28. Synderman, R. K.: Magnitude of the breast cancer problem. *In* Symposium on Neoplastic and Reconstructive Problems of the Female Breast. Saint Louis Mosby Company, 1973, pp. 1–4.
29. Snyderman, R. K. and Guthrie, R. H.: Reconstruction of the Female Breast Following Radical Mastectomy. Plast. Reconstr. Surg., 47:565, 1971.
30. Tai, Y. and Hasegawa, H.: A Transverse Abdominal Flap for Reconstruction after Radical Operations for Recurrent Breast Cancer. Plast. Reconstr. Surg., 53:52, 1974.
31. Thorek, M.: Plastic Surgery of the Breast and Abdominal Wall. Springfield Thomas, 1942.
32. Urban, J. A. and Castro, E. B.: Selecting Variations in Extent of Surgical Procedure for Breast Cancer. Cancer, 28:1615, 1971.
33. Wekler, M. R. and Oneal, R. M.: Areolar Sharing to Reconstruct the Absent Nipple. Plast. Reconstr. Surg., 51:176, 1973.
34. Wiemer, D. R. and Freeman, B. S.: Bilateral Reconstruction of the Nipple-Areola Complex. Plast. Reconstr. Surg., 58:310, 1976.

DISCUSSION

DR. FRANCIS E. ROSATO (Norfolk, Virginia): I'd like to thank Dr. Lynch for reminding us all that breast reconstruction can be done following mastectomy for cancer. It can be done effectively, and it can be done without hampering detection of recurrence.

We have had some experience at Eastern Virginia Medical School with our plastic surgery consultant, Dr. Charles Horton, over the past several years, and have accumulated some 40 patients who underwent reconstruction following an antecedent mastectomy that was done for cancer. It has required on the average 2.8 operations to complete the reconstruction, and with an average follow-up time at this moment of two years, there have been two recurrences to date.

Our major problem initially was with capsular contraction. This was when the prostheses were placed in a subcutaneous position. But this has not been as much of a problem recently, (slide) note now that the prostheses are placed in a submuscular position; and this is an option which is generally possible now, since most surgeons are doing muscle-sparing mastectomies.

I think a major question that arises in regard to reconstruction relates to the safety of this procedure in terms of host responsiveness. We have studied 60 rats who received lethal injections of transplantable mammary tumor, which uniformly produced tumors, which you can see here, (slide) and then all the rats underwent excision of their tumor and in half a miniprosthesis was placed. This is probably the smallest prosthesis ever manufactured by the manufacturer.

We found that in the group who received the prosthesis following their mastectomy there was no difference in lymphocyte reactivity, as measured by a lymphocyte cytotoxicity study; namely, the lymphocytes from the rats who received the prosthesis as effectively killed tumor cells in an *in vitro* preparation as did the lymphocytes in the animals who underwent excision alone.

We also found no difference in recurrence rate of tumors or in the survival pattern of the rats, regardless of whether or not the prosthesis was placed. Therefore, we think that the answer to the question "Does the placement of a prosthesis in an individual undergoing excision of a tumor adversely affect immune responsiveness?," at least in this small study done in rats, is definitely no.

I think this is an area of surgery which is now receiving appropriate attention, and one that deserves close cooperative effort between the surgeon, the plastic surgeon, and, certainly, the patient.

DR. HERSCHEL A. GRAVES, JR. (Nashville, Tennessee): Relative to Dr. Lynch's remarks concerning radical mastectomy, I agree that the majority of malignant breast tumors can be very adequately removed through a transverse elliptical incision and that those fibers of the pectoralis major muscle arising from the clavicle can be left in place without compromising the completeness of node dissection.

As general surgeons we are going to be called upon with increasing frequency to discuss the advisability of postmastectomy reconstruction with these patients. Only last week a 63-year-old woman inquired about a prosthesis insertion as her last mastectomy suture was removed.

A few months ago I was asked by Dr. Kirkland Todd, a plastic surgeon in Nashville, to participate in performing one of the Jurkiewicz procedures in which the omentum is freed from its colic and splenic attachments and is swung up to the anterior chest wall to cover a prosthesis and accept a split skin graft. We have now done four of these procedures and are enthused about the contour that has been obtained in these patients. I'd like to show a few slides of our first patient.

(Slide) As Dr. Lynch mentioned, the type of reconstruction is dictated a great deal by what is present on the other side. This lady had undergone a full-fledged radical mastectomy 12 years previously, and desired reconstruction.

(Slide) This is the prepped patient.

(Slide) This was made after we had made a right paramedian incision and freed up the omentum from the colon and spleen, leaving its attachment to the greater curvature of the stomach thereby preserving its blood supply. The outline above is the old mastectomy scar that was to be excised, and in general the size breast that we wanted to reconstruct.

(Slide) This is after Dr. Todd had placed the prosthesis.

(Slide) In some of these patients we have removed the xiphoid. In others it has not been necessary, and we simply make a subcutaneous tunnel from our paramedian incision up to the breast wound and place the omentum over the prosthesis.

(Slide) This is the split graft in place. All four split grafts have taken well to the transplanted omentum from the upper abdomen.

(Slide) And this is only about a month after surgery, and since then a little of the swelling above the graft has regressed and it looks even better now than it did then. A nipple reconstruction can be done later, if she desires.

(Slide) And this is another view of the same patient. We think that we are getting good results with this procedure.

I have one other patient that I would like to show you, (slide) which my plastic surgeon friend really didn't want me to show, but I thought it was so intriguing that I'm going to anyway.

This is a woman, about 50, who had very large breasts, although she was not generally obese. She was left with a very pendulous breast, and rather than reduce this and place a prosthesis on the other side, he elected to make two out of one, as follows:

(Slide) This shows the pre-op and immediate post-op status.

(Slide) Although a bit of the split graft was lost inferiorly, it healed well with appropriate debriding.

(Slide) In the sitting position about three months after surgery, these breasts look amazingly good. I think it may be a useful procedure in the exceptional patient under these circumstances.

DR. STEPHEN R. LEWIS (Galveston, Texas): I must admit, I disagreed with the first sentence Dr. Lynch wrote, from then on I was most impressed with the material he presented to us today.

I think, just to recapitulate a few of the things he has pointed out to us which are very important: First, this is the most common type of cancer in the female; that at least 6% to 10% of all women who live to the age of 85 or less will develop it. This means that approximately one in 15 of all women are going to have cancer of the breast. There are about 60,000–70,000 new cases of cancer of the breast per year, of which 40,000 have either a radical or a modified radical mastectomy.

I think what we forget sometimes as surgeons is that the psychological problems that go with breast removal may be almost as significant to the patient as the hopeful curative surgery. The fear of deformity may be the reason that so many patients delay getting surgery for breast lesions plus when they palpate their own lesions, they worry about a possible malignancy.

In view of these statistics, and its importance to the patient that preoperatively, every surgeon should be able to counsel these patients as to all potentials for reconstruction. I disagree with Dr. Lynch that only 20% request the rehabilitative surgery as it appears in our series close to 50%.

I think as improved techniques are available that at least 50% of your patients who are going to have ablative surgery are going to request some form of reconstructive surgery in an attempt to help them.

Those of you who have patients with external prostheses have probably lost them in the swimming pool or are uncomfortable for other reasons.

Secondly, I do recommend that we all consider organizations such as Reach for Recovery. In those patients who have had radical surgery for any type of cancer, and especially breast cancer, Reach for Recovery in breast cancer has been significantly psychologically beneficial to them in coping with their problems. We should all consider this for our patients.

Thirdly, reconstructive surgery for the modified radical type procedure is totally different from the extremely radical procedure. We cannot swing local flaps routinely on the very radical type of breast case. We can utilize, as we did in World War II and other times, a distant flap. And I'd like to show just a few cases of the distant flap, if I may, please.

(Slide) I recommend that the woman who has the radical mastectomy elect whether she wants further surgery or not. Here is a lady whose ribs are showing very well. She's had a vertical scar, rather significant loss of tissue, and the utilization of a tube pedicle from the inguinal area plus reconstruction using a breast sharing procedure as the nipple-sharing procedure from the other side, and then minor revisions.

It's not perfect, but every patient must realize that what we do as reconstructive surgeons is not going to give absolute symmetry. But by reduction, as Dr. Lynch has mentioned, we can reduce the other breast and make it somewhat better.

(Slide) One of our surgeons' wives here in the audience—the use of a tube pedicle after radical mastectomy, the tube used here, is one of the ways to fill the infraclavicular or the axillary area by removing the epidermis and the superficial dermis, take the fat and the dermis, and hide it up into the infraclavicular area, or the axillary area, and fill it out, and then later fill in the breast with an implant. This, plus minor reconstruction on the scarring, gave her good symmetry between the two breasts.

I think the most important thing is that your patients must realise and understand that the ultimate goal is to look good in clothing, not in the nude. After a successful reconstruction, she should not require any type of external prosthesis, and she should look good in both sport clothes and, hopefully, if they are as good as Dr. Lynch's—not mine—look good in a bikini.

There is no universal agreement as to when to select the time of operation for these patients, and, as such, I must ask Dr. Lynch a few questions.

In those patients in which the pectoralis muscle has been left attached, do you cut the distal attachment to minimize tension on the implant, if you are doing a subpectoralis implant?

Second question: Is there higher capsular contraction of implants following this type of reconstructive surgery, when one puts a foreign material into the area, than following a routine augmentation or subcutaneous mammoplasty?

And thirdly, does he feel that there is a necessary waiting period in the absence of those patients with intraductal carcinoma, or minimal, with no nodes, the T-1 and 0 type of problem, or can we go ahead and reconstruct them immediately?

And fourthly, what is against taking the nipple in the average malignancy, transplanting it to the inguinal area, and utilizing it in that function?

I do think that Dr. Lynch has shown us today, that this type of a case can be successful.

DR. MAURICE J. JURKIEWICZ (Atlanta, Georgia): I agree with Dr. Lynch. Arterialized flaps, whether they be skin, omentum, muscle, or skin and muscle, have made breast reconstruction possible, but, as Frank Spencer pointed out this morning, the eternal question is: Does the operation do good, or does it do harm?

I believe that with our present state of knowledge of cancer of the breast, patient selection and timing are of critical importance. Only in those patients in whom there is no consideration of adjuvant therapy: radiation, or chemotherapy, should reconstruction be carried out early, in my opinion. In no way should reconstruction interfere with the primary objective, the total extirpation of the disease, or as long a disease-free interval as possible.

In those patients who have been irradiated, the hazards of attempting to elevate the skin, or rotate local skin flaps, and insert a prosthesis, are great. Under these circumstances, we have come to use the latissimus dorsi myocutaneous flap. I am indebted to Dr. Otto Brantigan, of the Southern Surgical Association, who called my attention to the possibilities of transposition of the latissimus dorsi, in a paper entitled "Evaluation of Hutchins' Modification of Radical Mastectomy for Cancer of the Breast." This was published in 1974.

Actually, Hutchins' operation was originally described by Tanzini, in a paper entitled "A New Procedure for Amputation of the Breast for Cancer," published in the *Archives of Langenbeck* in 1896.

Both Hutchins and Tanzini undermined posterior skin flaps over the latissimus, thus depriving that particular area of skin of its blood supply, and inviting wound complications, which operation was designed to alleviate known wound complications.

(Slide) The blood supply to the posterior skin over the latissimus, comes from perforators through the latissimus itself; so that if one undermines that particular skin, necrosis may ensue. In patients with very tight skin over (slide) the thoracic wall, and where a fair amount of skin which has been resected, we have used the latissimus myocutaneous flap to bring needed tissue into the deficient area.

(Slide) It will fill in the axillary defect, as well as provide that amount of skin needed over the mound itself. In one stage, therefore, with a nipple-sharing procedure, the breast can be reconstructed.

(Slide) In the last year we have done 42 such reconstructions at Emory University Affiliated Hospitals. Seventeen have been latissimus flaps, five have been transverse abdominal flaps, four omentum and in 16, patients have been reconstructed simply by creating a mound. Tip necrosis occurred in one flap, of no consequence.

I would ask one question. Dr. Lynch mentioned that he would not do the reconstruction in a patient that had extensive axillary involvement. I'd like to know what "extensive" means.

Dr. John B. Lynch (Closing discussion): In response to Dr. Rosato's discussion, I would like to express my appreciation for bringing to our attention some scientific data to suggest that the use of implants in reconstruction does not in any way impair the patient's ability to withstand the possibility of recurrence. I don't think there is any scientific data that supports the concept that reconstruction may in some way promote a recurrence in human patients, but you continue to see it written in the literature and I think it's very refreshing to see someone taking it to the laboratory and trying to put some scientific numbers on it.

In response to the question about the subpectoral placement of this implant, this, of course, is not possible in the classical radical, since it's gone. The majority of our patients have had a classic radical. Even in the ones who have not, I have preferred to stick with the subcutaneous placement of the implant, because of some distortion that can occur with movement of the shoulder and chest if you have a submuscular implant.

The subcutaneous placement does, I think, increase the possibility of complications, and this is where I think the introduction of the routine intraoperative use of fluorescein for evaluation of the circulation in the skin flaps has been essential in reducing the complications to a minimum.

In response to Dr. Graves, I would like to congratulate you on some very beautiful cases. I am very much aware of the technique of using the omentum over a prosthesis with a skin graft for one stage reconstruction of the breast mound. We have used the omentum in reconstruction of two patients with chest wall defects following radiation necrosis of the chest wall. I have not used it in patients who have come under our care for reconstruction following radical mastectomy, but can certainly visualize a patient with extensive postoperative x-ray changes in the skin, where, as Dr. Jurkiewicz mentioned, this might be the only local arterialized flap that's available for a one-stage reconstruction of the breast mound; and I think the use of the omentum for this and other purposes has been a very positive contribution.

As far as Dr. Lewis is concerned, I think his reference to the fact that only 20% of the patients have requested reconstruction in the past, quite honestly, is related to the fact that we've done it so poorly that the surgeons haven't sent them over, and I don't blame them, for looking at some of my older cases. I think that is changing. And, I think, as we can do a better job, it will be better accepted. I would like to also congratulate you on a much better job with distant pedicle flaps than most of us have accomplished.

In response to the question about whether the incidence of fibrous capsular contracture is more common in these patients or not, this is a problem we have with all of our breast reconstructions. I don't think there are enough patients in this group to make any evaluation as to whether the incidence is higher in these patients or not.

In response to the question about an appropriate waiting period, I feel that in minimal disease which appears to be adequately controlled locally there is no apparent advantage to waiting an arbitrary period of time. This comes back to the point that Dr. Jurkiewicz made; that is, careful selection of patients.

As far as Dr. Jurkiewicz is concerned, I couldn't agree with him more that the primary objective in this disease is to cure the patient. And I couldn't agree with him more that the selection of patients is critical. Most of the ones that I have seen have been ones in whom the surgeon felt like there was a good chance that the disease was controlled locally, or I probably would not have seen them in the first place.

As far as Josh's question about what constitutes extensive axillary involvement, I'll probably have to discuss this with him in the hall since it will probably take some time.

The Prevention of Bypass Enteritis After Jejunoileal Bypass for Morbid Obesity

T. BRANNON HUBBARD, JR., M.D., PH.D.

The symptoms of bypass enteritis are disabling sequelae in many patients after jejunoileal bypass. This is a preliminary report of efforts to devise a valve to prevent reflux into the bypassed intestine after jejunoileal bypass. Valve I (42 cases) was formed by dividing the ileum, everting the proximal end as one matures an ileostomy, and inserting this into the distal ileum. Only 12 of these valves were competent. Valve II (six cases) was formed by dividing the ileum and merely inserting the proximal bowel into the distal, allowing it to evert spontaneously as with an unmatured ileostomy. In two cases the valve was competent, but four cases became obstructed and this valve is mentioned only to be condemned. Valve III (19 cases) is similar to an isoperistaltic Kock valve, except that the intussuscepted ileum is first divested of its mesentery. All such valves have been competent. All 33 patients with a competent valve have been free of the stigmata of bypass enteritis, whereas 54% of 156 patients showed the symptoms of enteritis after conventional jejunoileal bypass.

THE RESULTS AND COMPLICATIONS of jejunoileal bypass for morbid obesity have been described by numerous authors, including the recent report by Scott et al.[15] This paper addresses itself to a group of postoperative sequelae which are grouped under the heading of bypass enteritis and are characterized as follows.

There may be excess intestinal gas, frequently malodorous, often with a chronically distended abdomen in spite of weight loss, so that some women complain of appearing pregnant. There may be intermittent explosive diarrhea, as described by Passaro et al.[11] There may be pseudo-obstruction with pain, abdominal distention, fever, and markedly dilated colon as described by Barry et al.[2] This may progress to pneumatosis intestinalis and pneumoperitoneum, as described by Ikard et al.[7] Finally, there may be continual, prolonged malnutrition and hypoproteinemia possibly due to active loss of albumin from the bypassed intestine, as described by Drenick et al.[3]

From the Department of Surgery of the University of Maryland and Mercy Hospital, Baltimore, Maryland

In a personal experience with 156 intestinal bypass procedures, (end-to-side, 16 cases; end-to-end, 140 cases), followed for 17–60 months, 84 patients (53.8%) complained of intolerable, malodorous gas, of whom 30 (19%) presented with chronically distended abdomens. Thirty-eight patients (24.3%) experienced episodic diarrhea or pseudo-obstruction. Three of these developed pneumatosis intestinalis, one of whom developed pneumoperitoneum.

The problem of malodorous gas has not been stressed in the literature and is elicited as a rule, only by asking a patient specifically about it. Most patients seem reluctant to bring the matter up themselves. However, it is a symptom of no little importance. The personal and marital life of some patients is seriously threatened. Secretaries are reluctant to work in a room with others. Figure 1a shows a patient with chronic bloating 24 months after a bypass. He refuses to go to a movie or restaurant unless he is on a course of antibiotics, due to the odor of the gas. Once an extrovert, he now describes himself as an introvert. Figure 1b is of his abdominal x-ray showing massively dilated large and small bowel. Though occurring daily in this patient, the film may be easily confused with an abdominal catastrophe.

The majority of patients after intestinal bypass are happy with their weight loss, but one wonders why when so many suffer from these symptoms. Although their exact etiology is presently obscure, it appears probable that bacterial overgrowth secondary to reflux and stasis in the bypassed intestine is responsible. This is suggested by the fact that the symptoms usually respond to antibiotic therapy, including Metronidazole. However, over a lifetime after a bypass procedure, it is apparent that continued, repeated antibiotic therapy is an unsatisfactory answer for the patient and

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests: Mercy Hospital, 301 St. Paul Place, Baltimore, Maryland 21202.

Submitted for publication: December 8, 1977.

0003-4932-78-0500-0502-0085 © J. B. Lippincott Company

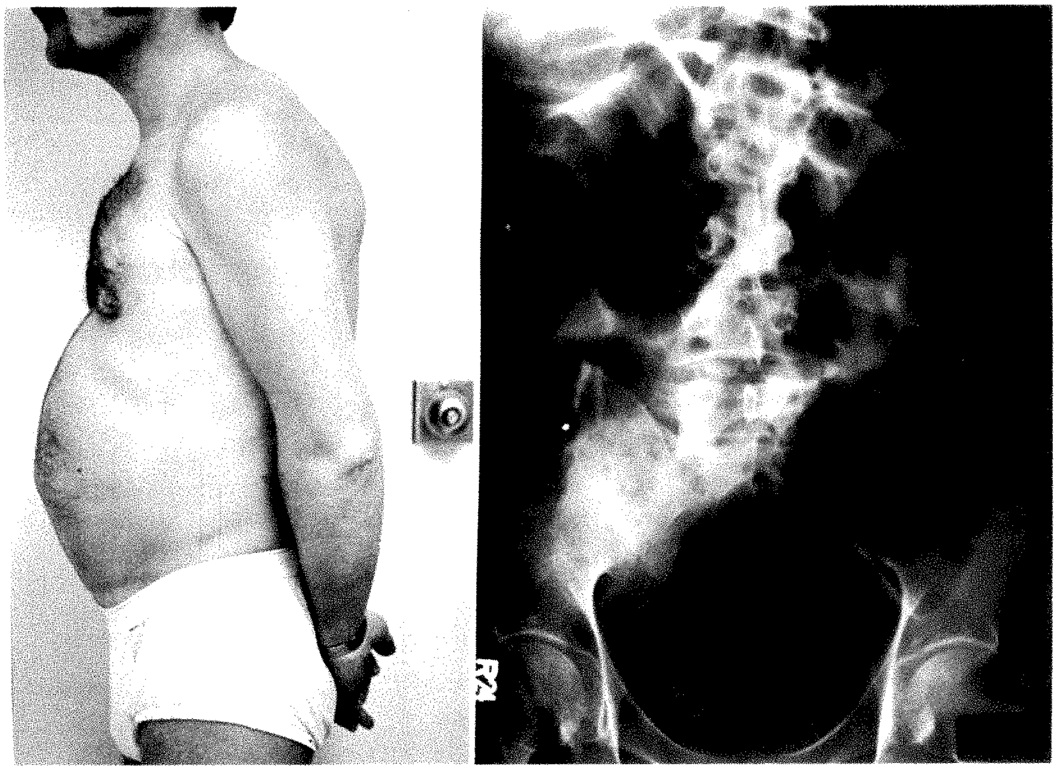


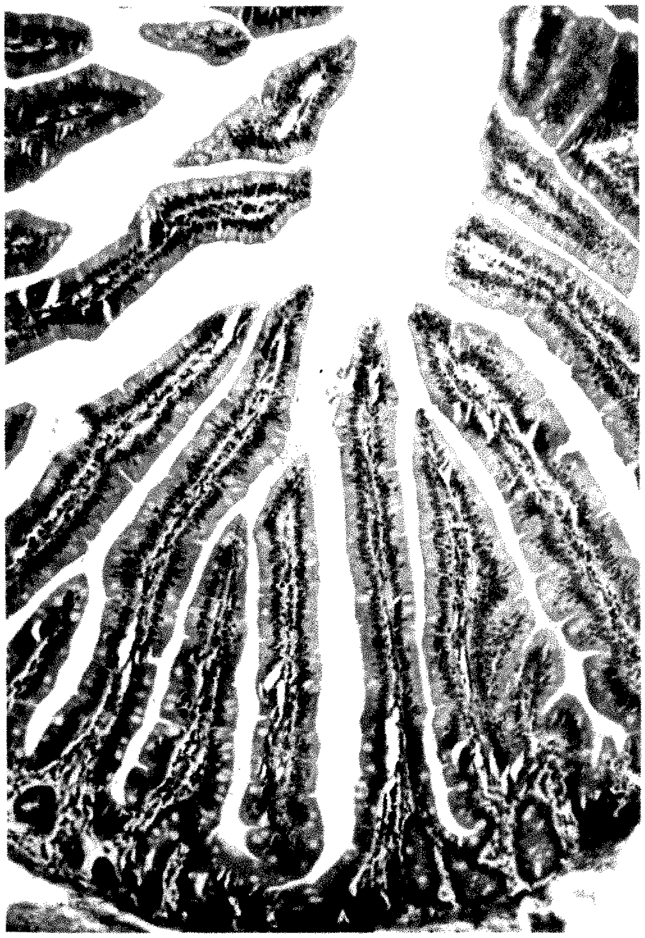
FIG. 1. (a) A patient two years after bypass showing chronic bloating. (b) Abdominal x-ray of same patient showing gas filled large and small bowel.

that the continued insult to the bypassed intestine cannot be comfortably tolerated over several decades. Grossly on re-exploration this bypassed bowel is markedly dilated, edematous, and thickened with a cloudy, roughened serosa. Figure 2 depicts the normal ileal mucosa compared to sections of two bypassed ileal segments. The blunted villi, submucosal infiltration, loss of polarity of the mucosal cells, and marked increase in mucin secreting cells is apparent.

That the ileocecal valve acts as a barrier to the bacteriologic flora of the colon is well known. Glassman[4] and Richardson and Griffen[12] have shown that mucosal valves in the intestines of dogs act as bacteriologic barriers. If reflux into the bypassed intestine could be prevented, the above described sequelae of intestinal bypass might not occur. This paper is a preliminary report of the development of an antireflux valve and the short-term results.

Valve I

Zheng et al.,[17] in 1976 described a competent intestinal valve formed by simply dividing the intestine and telescoping the proximal end into the distal. The tele-



FIGS. 2a–c. Photomicrographs of (a) normal ileal mucosa and (b and c) the mucosa of the ileum of two cases with bypass enteritis. Shortened villi, mucin secreting cells, and submucosal infiltration are apparent. (H & E stain ×100).

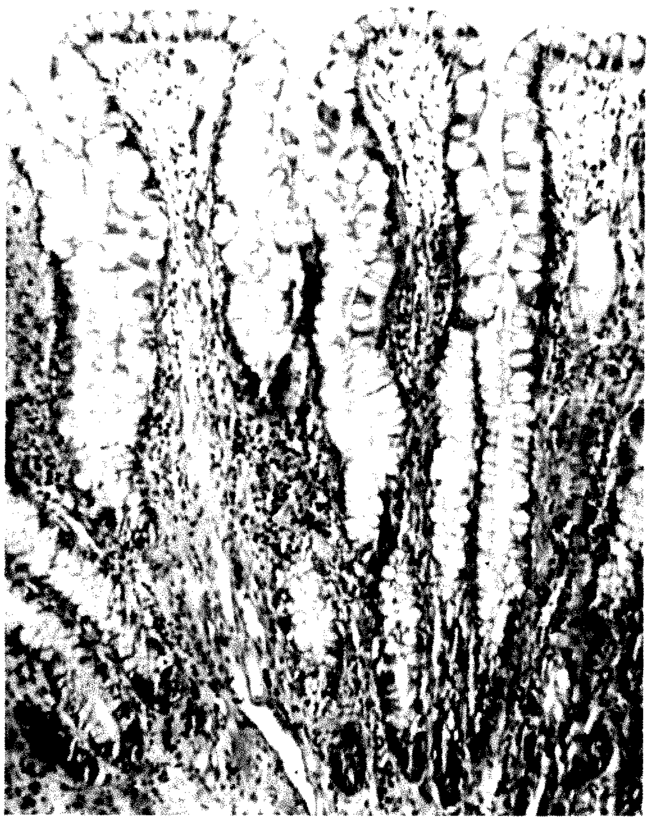


FIG. 2b. See legend for Figures 2a–c.

scoped end was allowed to evert spontaneously just as with an unmatured ileostomy, (Fig. 3). Shrum[13] in 1964 described a similar procedure as a means of forming an ileocolostomy. Both authors stated that in the dog no obstruction occurred and that clinical application was being considered. We were reluctant to adopt this procedure since in the case of the unmatured ileostomy one frequently saw stricture formation at the junction of the skin and ileum. We, therefore, utilized a similar procedure except that the valve was matured at the time of surgery. Two centimeters proximal to the site of the future end-to-side jejunoileostomy, the ileum is divided. The proximal end is divested of its mesentery for approximately five centimeters. The serosa of this segment is abraded with the scalpel to promote adhesions and the bowel is everted on itself and secured with sutures of 4-0 dexon between the everted edge and the seromuscular coat of the proximal bowel. Two longitudinal sutures of 4-0 chromic catgut are placed through both layers and tied loosely to prevent retraction of this nipple until adhesions are formed between the two layers. The nipple is then inserted into the distal ileum and secured with 4-0 silk sutures which incorporate the edge of the distal bowel, the edge of the everted bowel, and the seromuscular wall of the proximal bowel. An end-to-side jejunoileostomy is made just distal to the tip of this nipple (Fig. 4). Forty-two such valves have been formed, but only 12 have remained competent on follow-up of five to 18 months.

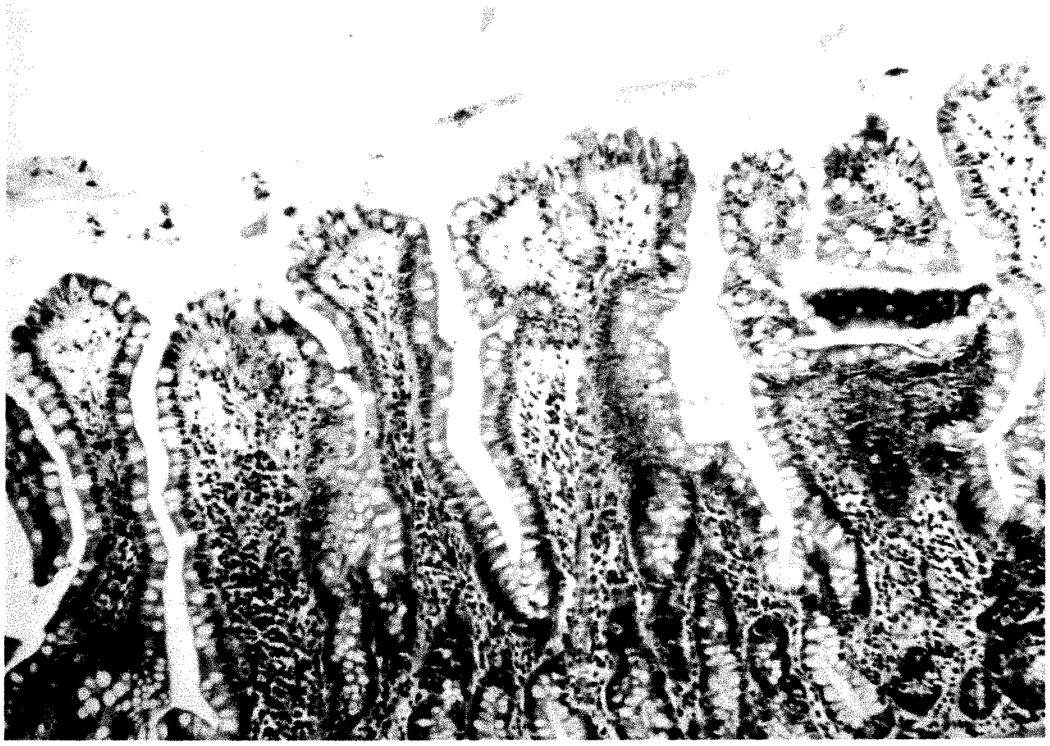


FIG. 2c. See legend for Figures 2a–c.

Valve II

The high incidence of incompetency of Valve I seemed to be due to the fact that the nipple, when divested of its mesentery, was necessarily quite short if it were to remain viable after being everted. Therefore, we finally had the temerity and lack of judgement, to form a valve similar to that described by Zheng,[17] foregoing mucosa to mucosa approximation, (Fig. 3). Six such valves were formed. The first two cases were competent and have had no problems. However, the next four cases all became obstructed 15–35 days after surgery, requiring resection of the valve. After this experience, belated correspondence with Shrum, who originally described the procedure, revealed that about 20 such ileo-transverse colostomies had been done clinically, with obstruction in approximately one fourth of the cases.[14] Since it is rare that an idea occurs in only one place, our own experience is reported here with some humility to prevent further trials of this procedure by others.

Valve III

The third, and apparently successful valve, is a modification of the Kock valve.[8] Two centimeters proximal to the site of the future end-to-side jejunoileostomy, the ileum is devascularized, staying close to bowel for approximately five centimeters, or until the midportion of the devascularized segment appears very slightly compromised. The serosal surface of this segment is then abraded with bone rasp or cautery. The incision is then made in the ileum for the future jejunoileostomy, and through this incision the midpoint of the devascularized segment is grasped with two sutures and intussuscepted distally. The proximal edge of this nipple is fixed to the adjoining intestine with interrupted sutures of 4-0 Ethiflex and two sutures of catgut are placed through the intussuscepted nipple to promote adherence of the two layers. A number 20F catheter is then passed proximally through the nipple and interrupted 4-0 Ethiflex seromuscular sutures are placed transversely to narrow the proximal ileum for a distance of approximately 4 cm to prevent retrograde reduction of the nipple. Approximately 15 cm of proximal ileum are plicated to prevent traveling of the intussuscepted nipple. The end-to-side jejunoileostomy is then performed in the usual way (Fig. 5).

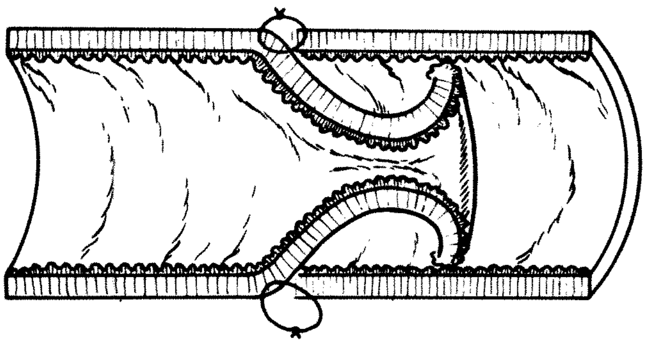


FIG. 3. The intestinal valve described by Zheng. The bowel is divided, intussuscepted, and allowed to evert spontaneously.

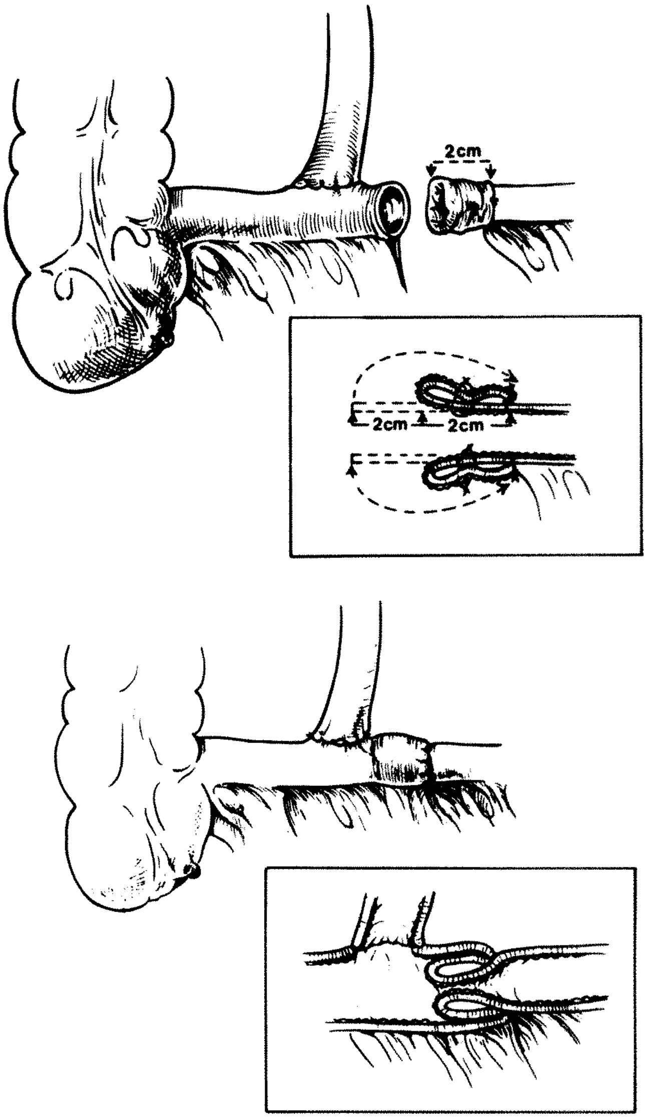
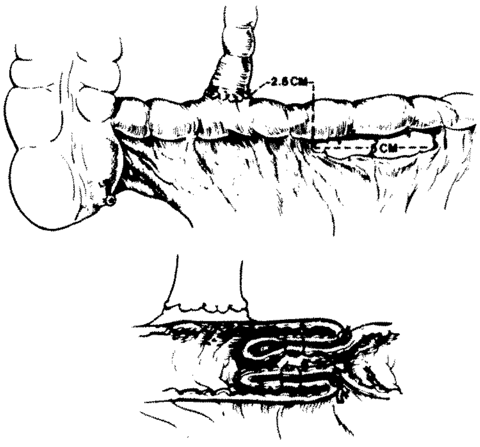


FIG. 4. Valve I (top) The ileum is divided and the proximal end is everted on itself. Valve I (bottom) The everted end is inserted into the distal bowel just proximal to the jejunoileostomy.

Nineteen bypasses have been formed in this manner and all valves have remained competent on follow-up of four to eight months. Figure 6 is of a small bowel series performed on such a patient. The valve appears as typical intussuscepted intestine.

In addition, three patients who after an end-to-end jejunoileostomy and ileotransverse colostomy suffered from malodorous gas, episodic diarrhea, and bloating have been converted to an end-to-side jejunoileostomy with such a valve. Such conversion was approached



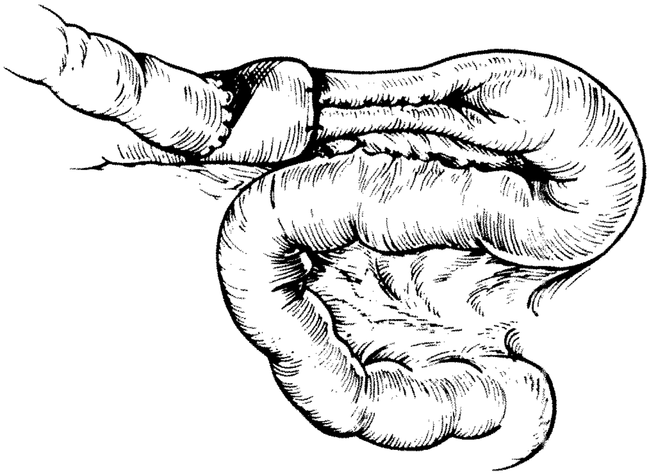


FIG. 5. Valve III (top) The future valve is devascularized and intussuscepted just proximal to the end-to-side jejunoileostomy. Valve III (bottom) The ileum just proximal to the valve is narrowed and an adjacent segment is plicated to prevent progression of the intussusception.

with some skepticism since the dilated, edematous bowel did not seem to lend itself to forming a satisfactory valve. These three patients, however, did not wish to continue as they were, to have their normal bowel continuity restored, or to undergo a gastric bypass. They desired to accept the possibility that the valve might not function satisfactorily. In two cases the valve has been competent, and in one has allowed reflux.

Results

The 30 patients with an incompetent valve (valve I) and the four patients whose valves were resected (valve II) have all pursued a course similar to the conventional end-to-side jejunoileostomy.

The 33 patients with a competent valve, either types I, II, or III, have only been followed for from four to 17 months. These results can, therefore, only be considered tentative, but their course has been remarkably asymptomatic. None of them have complained of malodorous gas, bloating or intermittent diarrhea. While losing an average of 4.0 Kg per month during the first year, their attitude and general health have been in marked contrast to the patient who had had a conventional intestinal bypass. Bowell movements after two months have ranged from one to eight per day, with an average of four per day. Serum albumin levels have ranged from 3.8 to 4.4 g per deciliter (average 4.0). Table 1 contrasts the incidence of symptoms of bypass enteritis in 156 conventional bypasses and the 33 cases with competent valves.

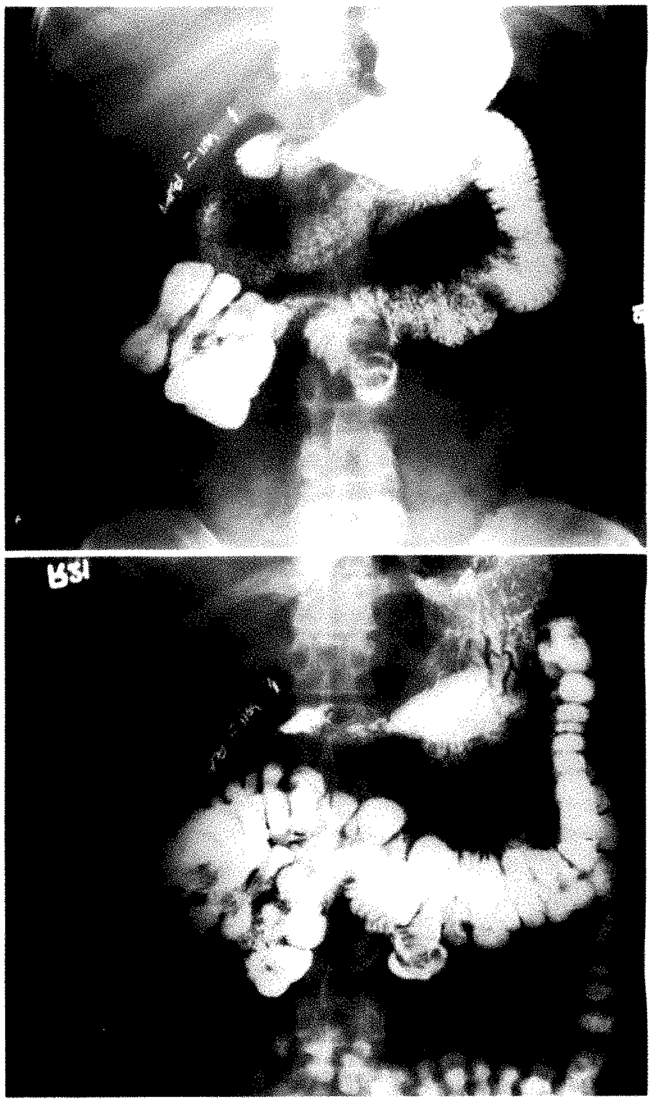


FIG. 6. A small bowel series showing a Type III Valve (top) at 15 minutes; (bottom) at 60 minutes.

One patient, who began drinking heavily after the bypass, developed hepatic dysfunction which necessitated taking down of the bypass. At re-exploration the entire bypassed intestine was small, empty and collapsed, in marked contrast to the dilated, thickened intestine usually seen in the bypassed intestine in its distal portion.

Of the three patients who were converted from an ileotransverse colostomy to a Valve III, the one with an incompetent valve has no change in her symptoms. Two, however, on follow-up of four and five months have had no more bloating, malodorous gas, or episodic diarrhea, and are well satisfied with the results.

Discussion

The most serious complication of jejunoileal bypass is hepatic failure. It is probable that the primary cause is protein–calorie malnutrition secondary to malabsorption. However, bacterial overgrowth in the bypassed segment could possibly accentuate the problem. O'Leary et al.[9] showed that after jejunoileal bypass dogs treated with Doxycycline retained normal hepatic morphology, whereas nontreated dogs developed fatty livers with centrilobular necrosis. Other studies comparing bypass and resection in dogs by Hyland et al.[6] and in rats by Viddal et al.,[16] showed less disturbance in liver function after resection, though there was no significant difference in liver morphology. Whether intestinal bypass in which there is no reflux into the bypassed segment will minimize the incidence of hepatic failure remains to be seen. However, the occurrence of one such case in these 33 patients suggests that hepatic failure is certainly not totally dependent on reflux into the bypassed segment.

Surgeons have for years searched for a method of simulating the ileocecal valve and it may be that the present valve (Valve III) is an answer. When made in the ileum of the dog, in continuity with the intact intestinal tract, no obstruction has occurred and no dilation of the proximal bowel. This does not mean that free passage of intestinal contents would occur in the human, for the danger of extrapolating results in the experimental animal to man is well shown by our experience with Valve II. The latter unfortunate experience emphasizes once again that in surgery of the intestinal tract, mucosa to mucosa approximation is a sine qua non if stricture is to be avoided.

The making of Valve III on first glance looks like a complicated, unnecessarily extensive procedure. In practice, however, it is not difficult and is probably safer than an end-to-end anastomosis. Most reports of large series of the latter procedure describe at least one case of anastomotic leak or stricture.

The jejunoileal bypass has been placed somewhat sub judice by the recent reports of Alden[1] and Griffin et al.,[5] comparing the gastric with the intestinal bypass. However, if a jejunoileal bypass is done, we believe that an end-to-side jejunoileostomy with an antireflux valve (Valve III), is the procedure of choice. It apparently prevents the sequelae of bypass enteritis. Its further effects must await longer follow-up.

TABLE 1. *The Incidence of the Symptoms of Bypass Enteritis after Conventional Jejunoileal Bypass and after Bypass with a Competent Valve*

	Conventional Bypass (156 Cases)	Bypass with Competent Valve (33 Cases)
Malodorous gas	84 (53.8%)	0
Episodic diarrhea or Pseudo-obstruction	38 (24.3%)	0
Bloating	30 (19.2%)	0
Pneumatosis intestinalis	3 (01.9%)	0

References

1. Alden, J. F.: Gastric and Jejunoileal Bypass, A Comparison in the Treatment of Morbid Obesity. Arch. Surg., 112:799, 1977.
2. Barry, R. E., Benfield, J. R., Nicell, P. and Bray, G. A.: Colonic Pseudo-obstruction: A New Complication of Jejunoileal Bypass. Gut, 16:903, 1975.
3. Drenick, E. J., Ament, M. E., Finegold, S. M., et al.: Bypass Enteropathy, Intestinal and Systemic Manifestations Following Small Bowel Bypass. JAMA, 236:269, 1976.
4. Glassman, J. A.: An Artificial Ileocecal Valve. Surg. Gynecol. Obstet., 74:92, 1942.
5. Griffen, W. O., Young, V. L. and Stevenson, C. G.: A Prospective Comparison of Gastric and Jejunoileal Bypass Procedures for Morbid Obesity. Ann. Surg., 186:500, 1977.
6. Hyland, G., Stein, T. and Wise, L.: Abnormalities of Liver Function Following Extensive Jejunoileal Bypass and Resection in Rats. Surgery, 81:578, 1977.
7. Ikard, R. W.: Pneumatosis Cystoides Intestinalis Following Intestinal Bypass. Am. Surg., 43:467, 1977.
8. Kock, N. G.: Intra-abdominal "Reservoir" in Patients with Permanent Ileostomy: Preliminary Observations on a Procedure Resulting in Fecal "Continence" in Five Ileostomy Patients. Arch. Surg., 99:223, 1969.
9. O'Leary, J. P., Maher, J. W., Hollenbeck, J. I., et al.: Pathogenesis of Hepatic Failure after Obesity Bypass. Surg. Forum, 25:356, 1974.
10. Payne, J. H. and DeWind, L. T.: Surgical Treatment of Obesity. Am. J. Surg., 118:141, 1969.
11. Passaro, E. Jr., Drenick, E. and Wilson, S. E.: Bypass Enteritis: A New Complication of Jejunoileal Bypass for Obesity. Am. J. Surg., 131:169, 1976.
12. Richardson, J. D. and Griffen, W. O.: Ileocecal Valve Substitutes as Bacteriologic Barriers. Am. J. Surg., 123:149, 1972.
13. Shrum, R. C., Williams, G. S., Allen, M. S., Jr., et al.: Simplified Technique of Ileocolostomy. Surg. Forum, 15:299, 1964.
14. Shrum, R. C.: Personal Communication, 1977.
15. Scott, H. W., Jr., Dean, R. H., Shull, J. H., et al.: Results of Jejunoileal Bypass in Two Hundred Patients with Morbid Obesity. Surg. Gynecol. Obstet., 145:661, 1977.
16. Viddal, K. O. and Nygaard, K.: Intestinal Bypass in Rats. Chir. Gastroenterol., 11:213, 1977.
17. Zheng, H., Onishi, S., Tanigawa, N., et al.: Manometric Evaluation of an Artificial Intestinal Valve. Arch. Surg., 111:578, 1976.

Discussion

Dr. Richard T. Shackelford (Baltimore, Maryland): Dr. Hubbard, I am particularly interested in your successful results with the use of an isoperistaltic Koch type valve to prevent reflux. At the Loch Raven Veterans Hospital in Baltimore Dr. Kieffer and his staff perform many jejunoileal bypasses for obesity and prefer to use this nipple-type valve to prevent reflux.

Recently a complication, that was new to our experience, occurred three years following a jejunoileal bypass operation for morbid obesity.

In 1974 a 52-year-old morbidly obese man was admitted to the Veterans Hospital. He weighed 400 lbs. Dr. Kieffer performed a 14 and four inch standard jejunoileal bypass procedure. The blind end of the isolated jejunoileal segment was sutured to the transverse mesocolon in order to fix it in its normal position. Recovery from the operation was uncomplicated. During the following two and one-half years he lost 200 pounds, went from 400 down to 200 pounds, at which weight he stabilized and felt fine. However, in 1977, three years after the operation, he reentered the hospital with the complaint of steady abdominal pain and one mild vomit. Examinations revealed no distention, only moderate abdominal tenderness, no abnormal radiologic, laboratory, hematologic or other findings. After several days observation an exploratory laparotomy was performed by Dr. Ricotta, the senior surgical resident, and Dr. Kieffer. An intussusception of the distal portion of the isolated segment of jejunoileum was found. The middle third of the segment had intussuscepted antegrade into the distal blind-end-third. The proximal third of the isolated segment, which opened into the functioning ileum, was not involved and its value-like stoma was patent.

The intussuscepted distal two-thirds of the isolated segment was resected. The remaining proximal remnant was left in place and its cut end was closed with sutures.

(Slide) This is the specimen before it had been opened.

(Slide) This is the opened specimen, showing the middle third intussuscepted into the distal third.

The patient's recovery was uneventful. During the following nine months his weight was stationary, he was asymptomatic and seemed well. At the end of nine months he reentered the hospital with exactly the same symptoms as on his previous admission: A steady, severe abdominal pain; no other detectable signs. As before, x-ray and laboratory studies provided no clue to the diagnosis. Because of the similarity to his previous intussusception, reoperation was performed. The remaining proximal remnant of isolated bowel was found to be intussuscepted antegrade into itself. Since his weight had remained stationary, he was feeling well, and had been very happy until the present attack, the remaining isolated bowel was removed and the opening in the ileum was closed with sutures.

Again he recovered rapidly and completely, has maintained his 200 pound weight loss and is very happy with the results.

In the past week he has developed a lesion in the rectum which is suspected, but not proven, to be carcinoma which seems to be unrelated to his previous procedures. Despite these complications he remains happy.

The important point I want to emphasize is that in both of these episodes we were unable to establish a preoperative diagnosis. He had severe abdominal pain but x-ray examination showed no distention, blood studies and temperature were normal. I suggest that if a patient with a jejunoileal bypass for obesity has an unexplainable steady abdominal pain, remember that it may be advisable to perform an exploratory laparotomy.

The final point is that in Sir Ashley Cooper's *Book of Surgery*, published in 1814, or thereabout, he mentions that "An empty segment of bowel invites intussusception." I offer that for you all to think about.

Dr. M. Bert Myers (New Orleans, Louisiana): I rise only to confirm that an intussuscepted bowel is a leakproof valve, and that it is permanent, at least in the dog.

About 20 years ago we attempted to make a leakproof gastrostomy, using a segment of jejunem which had such an intussuscepted loop in it, and it worked very well.

(Slide) This shows a stomach with a loop of jejunem here at one end that was hooked to the skin. This shows the stomach at a year. It was removed, both ends were tied, and it was filled with water. This shows that pressure on it fails to cause leakage. And during this time you could feed the dog at any time through the jejunal look, since the valve was pointed toward the stomach.

(Slide) This shows the length involved. The only technical points we found were that the valve had to be at least 5 cm long, and had to be scarified, or it would come undone. But it is a satisfactory method, and it is leakproof, and it will last at least a year in the dog.

Dr. H. William Scott, Jr. (Nashville, Tennessee): I'd like to congratulate Dr. Brannon Hubbard and his associates on this approach to the problem of so-called bypass enteritis. Before entering into this, let me point out to you a very fundamental fact about jejunoileal bypass; and that is, it interferes profoundly with fat absorption. And if the patient continues to ingest freely large amounts of fat, he will develop, characteristically, a syndrome of bloating, foul-smelling flatus, and exacerbation of diarrhea, which is fundamentally steatorrhea. I think it's important to differentiate this "normal" response to intestinal bypass from some kind of mechanical abnormality or other changes in the bypassed segment of bowel.

If you can convince these patients to stay away from fat in the diet and avoid milk, a great majority of the bloating, flatulent, postprandial problems can be eliminated, and I don't think you need to make a nipple valve.

We have been interested very much in the problems, the complications, of jejunoileal bypass; and certainly there are many.

(Slide) In a series of over 200 massively obese patients that have been submitted to jejunoileal bypass, we have had no instance of intussusception. The upper segment of the bypassed bowel must be securely sutured to the fibrous mesocolon, or mesentery, or to the wall of the bowel itself, to prevent jejunoileal intussusception. I think Dr. Shackelford's case of retrograde intussusception must be extraordinarily rare.

In these 200 patients, the overall good results have been in the usage of 66%, and in those individuals who have had the more recent dimensions of end-to-end jejunoileostomy, in which 18 to 20 inches of short bowel are produced, the results have been good in the range of 75%.

We have been greatly interested in the enterohepatic syndrome, as we prefer to call it, following intestinal bypass. (Slide) This comes, almost certainly, *not* from the shortened bowel, which does not contribute greatly to this, except by inducing, temporarily, in the first few months after bypass protein-calorie malabsorption, but from the anastomosis of the bypassed segment of bowel to the colon that sets the stage for colonization of the bypassed ileum by colonic bacteria.

About 15% of the patients who have had this type of anastomosis will develop the problem of the so-called enterohepatic syndrome of clinical significance. What is it? How do you recognize it?

First of all, the patient develops a flu-like syndrome with nausea, anorexia, myalgias, bad taste in the mouth, a tendency to vomiting, and will have elevation of liver enzymes. On a technitium scan, the uptake of the isotope is diminished. And this syndrome will respond in the majority of patients, as Dr. Hubbard has brought out, to oral broad spectrum antibiotics; and Flagyl, we believe, is the antibiotic of choice.

(Slide) What we have done in the laboratory to try to get at the cause of the problem can be summarized briefly as follows: this slide illustrates a model in the dog of extreme shortening of the small bowel from pylorus to cecum of only ten inches of the duodenojejunal dimension, and six inches of ileum with end-to-end anastomosis; the bypassed bowel is anastomosed to the colon. Dogs with this preparation will uniformly develop cellular necrosis within the liver in a period of about six months.

(Slide) If one does exactly the same thing, but excises the bypassed segment of bowel, leaving no anastomosis of the bypassed bowel to the colon, dogs with an identical degree of bowel shortening do not develop cellular necrosis in the liver.

This confirms the work of Bonder and Pisesky, who have done a similar study.

(Slide) In lieu of excising the bypassed segment, which would be clinically radical, we have studied another variation; this is to close the upper end of bypassed jejunum, retain the bypassed jejunoileum within the abdomen, but exteriorize the distal end of the ileum as a mucous fistula. In animals with this preparation in studies still under way with exactly the same dimensions of bowel shortening, hepatic cellular necrosis has been seen at six months in only one of six dogs.

Although quantitative bacterial studies of the flora in bypassed bowel are underway, it is very difficult at this point to identify qualitative bacterial differences between these two preparations. We're not sure at the moment whether the hepatocellular injury is due to the absorption of toxic bacterial metabolites from the bypassed segment of ileum or from other effects of bacterial growth such as deconjugation of bile acids to a known hepatotoxic substance, such as lithocholic acid.

(Slide) I think we're getting at the same problem in a little bit different way than Dr. Hubbard has approached it, but in several patients who have failed to respond to broad spectrum antibiotics with the enterohepatic syndrome following jejunoileal bypass, we have now exteriorized—taken down the ileocolic anastomosis and exteriorized the ileum as a mucous fistula; and this has been accompanied by the elimination of the enterohepatic syndrome, with restoration of well-being and good health, in three patients in our series. Dr. Fred Preston in Santa Barbara first did this exteriorization procedure on a patient of ours about 18 months ago with a very good result.

Another approach to the problem, of course, is the more radical procedure of eliminating the bypassed segment totally, either primarily or secondarily, which I do not advocate.

I believe that Dr. Hubbard's approach is most commendable, but the thing that worries me (and I want to ask him about this) if he makes a really good nipple valve to prevent reflux, similar to the Kock valve continent ileostomy, will this valve be able to permit the passage of mucus from in the bypassed segment of bowel?

In the Kock valve, as all of you know, with the Koch ileal pouch, the valve has to be catheterized; otherwise, it is really continent, and does not permit passage of intestinal contents from the pouch. I'd like to hear Dr. Hubbard's comments on this.

Dr. T. Brannon Hubbard, Jr. (Closing discussion): Dr. Schackelford, that's a fascinating case. I cannot explain it, but in view of the reflux and retention of intestinal contents into the bypassed bowel, one wonders if the motility of this intestine might not somehow be disturbed. Your patient is, of course, a serendipitous clinical example of the most radical way of doing away with bypass enteritis.

Dr. Myers, I appreciated your confirmation of our valve. I think, though, I would like to emphasize again that the so-called Zheng valve worked beautifully in the dog but it does not work in the human and we cannot extrapolate everything from the experimental animal to man.

I particularly appreciate Dr. Scott's discussion about the, to me, enigmatic problem of the so-called enterohepatic syndrome. We have had one patient with such a problem in whom we brought out the distal end of the bypassed intestine as an ileostomy. However, this patient showed no improvement over a six weeks' period so we finally went in and reconstituted her normal intestinal continuity with rapid improvement in her nutrition and liver status.

As far as the patency of the valve is concerned, the one patient whom we have re-explored, the patient with liver failure, showed a bypassed intestine that was collapsed and empty with no evidence of stasis. In the dog, when the valve is made in continuity with the intact intestinal tract, there is no evidence of obstruction and the animal is able to eat and the intestinal contents go through the valve without apparent obstruction.

Announcement

The appearance of the code at the bottom of the first page of an article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per-copy fee through the Copyright Clearance Center Inc., P.O. Box 765, Schenectady, N.Y. 12301, for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

The Comparative Survivals of Alcoholics Versus Nonalcoholics After Distal Splenorenal Shunt

ROBERT ZEPPA, M.D., GEORGE T. HENSLEY, M.D., JOE U. LEVI, M.D., PAUL R. BERGSTRESSER, M.D.,
DUANE G. HUTSON, SR., M.D., ALAN S. LIVINGSTONE, M.D., EUGENE R. SCHIFF, M.D., PAT FINK, R.N.

From the Departments of Surgery and Pathology,
University of Miami School of Medicine
and Affiliated Hospitals, Miami, Florida

Survival after distal splenorenal shunt is appreciably better in nonalcoholic patients than in alcoholics. This increase in survival does not appear to be dependent upon the state of biochemical liver function or the severity of changes in liver histology since these latter were similar for both groups. We suggest that the poorer survival of alcoholics may be related to continuing alcohol toxicity, and that a possible reason for the failure to demonstrate this difference in survival after portacaval shunts may be due to the harmful effects of total portal diversion on the liver.

DATA ABOUT THE COMPARATIVE survivals of alcoholic versus nonalcoholic patients who have required portasystemic shunts are meager. A recent report by Kanel and his colleagues[4] has shown that survival rates are similar after therapeutic portacaval shunts regardless of the etiology of the cirrhosis. This finding is at variance with a report from our clinic[8] which suggested that patients with nonalcoholic cirrhosis, portal hypertension and bleeding varices demonstrated a greater probability of survival to the fifth postoperative year after distal splenorenal shunts than did alcoholics treated similarly.

The contradiction in these findings may be due to the different effects of the operative procedures *per se*. All of the patients in Kanel's report underwent total portasystemic diversion while in our patients, selective portal decompression was applied. On the other hand, it may be argued that preoperative disturbances in liver function and liver histopathology were worse in our alcoholic patients than in the nonalcoholics.

In order to answer this latter question, survival was computed by lifetable analysis[1] and the results of liver function tests were reviewed for 91 patients undergoing distal splenorenal shunts. Hepatic histopathology was examined in detail for 16 patients whose slides were selected by chance from the entire group.

Material and Methods

The indication for operation in these patients was bleeding. The average number of bleeding episodes was between two and three, while the average number of transfusions given was between six and seven. In all of the patients, varices were identified at endoscopy and/or by barium or angiographic studies. Liver biopsies were performed in all patients and cirrhosis was identified in all but three, two nonalcoholic and one alcoholic; all of whom had severe hepatic fibrosis and portal hypertension.

Fifty-two patients were classified as having alcoholic liver disease, based predominantly on history and supported (with the exception previously noted) by liver histology. Similarly, 39 patients were judged to have nonalcohol associated liver disease and portal hypertension. All patients were evaluated with liver function tests and hepatic panangiography. In no instance did a patient have in excess of two liters of ascitic fluid at the time of surgery and all patients underwent elective distal splenorenal shunts.

In view of the time and effort required for detailed histopathological comparisons, it was decided to evaluate a 20% sample of the histological material. Three of the 19 sets of slides chosen at random were second studies on the same patients, hence the sample size is 18% of the total. The slide sets were selected by chance and the pathologist (G. T. H.) was unaware of any history of alcoholism, liver function or survival of the patients. In the pathological evaluation an effort was made to estimate the extent of liver damage with emphasis on those features most likely to effect prognosis. Five morphologic features were chosen and graded.

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Supported in part by grant #RR00261 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

Submitted for publication: December 8, 1977.

0003-4932-78-0500-0510-0075 © J. B. Lippincott Company

TABLE 1. *Elective Distal Splenorenal Shunt (July 1971–June 1977)*

	Range	Mean	Normal
Age	17–70	48	
Tot. protein	5–10	7.4	6–8 gm%
Albumin	1–5	3.7	3.5–5.5 gm%
Tot. bilirubin	0.2–7.0	1.4	0.1–1.2 mg%
Alk. phos.	33–657	145	30–90 U/L
Sgot	8–99	54	7–40 U/L

Characterization of patient population.
Number of patients = 91.

1) Active chronic hepatitis was said to be present when piece-meal necrosis was seen and/or if the periphery of the nodules or persisting lobules were infiltrated by mononuclear cells, including plasmacytes. The infiltrates had to encroach on the hepatocytes. The severity of the process was arbitrarily graded into three steps, the number 1 representing the mildest; zero was assigned if the feature was absent.

2) Hepatocellular necrosis was said to be present if the cells showed definite pyknosis, karyorrhexis, or if Councilman bodies were observed. Clusters of lymphocytes or granulocytes were also taken as evidence of necrosis if they occupied large loci in the midst of fields of hepatocytes. Without morphometric methods, this feature was difficult to estimate and thus was divided into only two grades;[1,2] zero assigned if necrosis was not seen.

3) Scarring was recognized by the presence of deposits of collagen outside the portal tracts. Trichrome stains were used. Grade 1 scarring is septum formation without predominant bridging. Grade 2 had, in addition, prominent bridging and/or localized postnecrotic scars in small numbers. Grade 3 featured numerous postnecrotic scars as well as Grade 1 and 2 findings. Zero indicated liver biopsies without scars.

4) Sinusoidal destruction was graded from zero (normal sinusoids everywhere present) to three (no or rare sinusoids found). Grade 1 represents cirrhosis with regenerative nodules (sinusoids not counted!) but with well preserved lobular sinusoidal structures still predominant. Grade 2 was similar but regenerative nodules were numerous and expansive, with compression of the remaining lobular sinusoids.

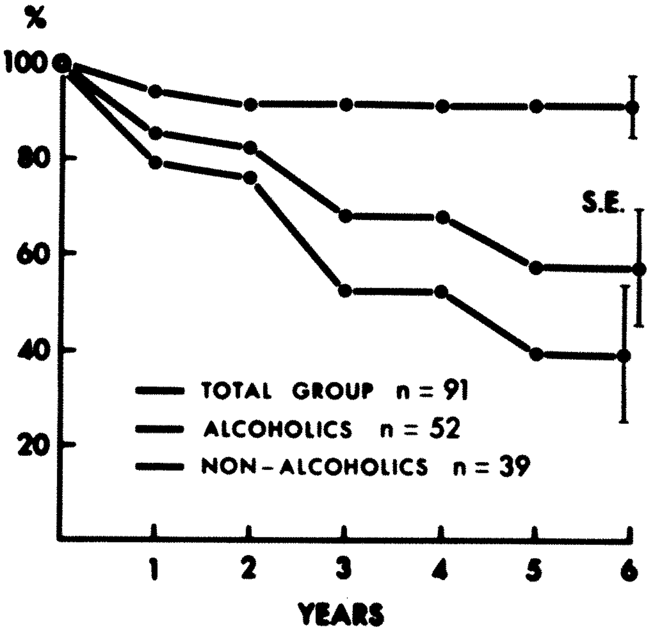


FIG. 1. The curve which displays the probability of survival for the entire group (n = 91, prob. surv. 57% ± 12% S.E.) is in the middle of the figure. The upper curve displays the nonalcoholic experience (n = 39, prob. surv. 89% ± 6% S.E.) and the lower curve, the fate of alcoholics (n = 52, prob. surv. 39% ± 14% S.E.).

5) Sinusoidal sclerosis refers to the deposition of fine collagen fibers beginning about the central vein and radiating centrifugally into the central reaches of sinusoids. It was stated to be present (1) or absent (0). The application of this method of grading the severity of the histologic alterations resulted in a composite score for each patient.

Results

The pertinent characteristics of the patient population are listed in Table 1. The wide range describing both age and biochemical status indicate the heterogeneity of this group. Clearly Child's Category C was represented in the cohort, if not by presence of ascites then at least by hyperbilirubinemia, hypoalbuminemia and elevation of serum enzyme activities. Despite this, such characterization was not a useful predictor of operative mortality. Only one patient died postopera-

TABLE 2. *Alcoholic Versus Non-alcoholic*

Variable	Alcoholic n = 52 Mean	Non-alcoholic n = 39 Mean
Age	50	46 (NS)
Tot. protein	7.5	7.1 (NS)
Albumin	3.7	3.6 (NS)
Tot. bilirubin	1.4	1.4 (NS)
Alk. phos.	114	183 $P < .01$
Sgot	48	60 $P < .05$

TABLE 3. *Survival vs. Nonsurvival*

Variable	Survivors n = 72 Mean	Nonsurvivors n = 19 Mean
Age	48	51 (NS)
Tot. protein	7.4	7.2 (NS)
Tot. bilirubin	1.4	1.5 (NS)
Alk. phos.	153	117 (NS)
Sgot	53	57 (NS)

Total group n = 91.

TABLE 4. *Survival vs. Nonsurvival*

Variable	Survivors n = 36 Mean	Nonsurvivors n = 16 Mean
Age	49	50 (NS)
Tot. protein	7.6	7.2 (NS)
Tot. bilirubin	1.4	1.4 (NS)
Alk. phos.	123	114 (NS)
Sgot	46	53 (NS)

Alcoholic n = 52.

TABLE 5. *Survival vs. Nonsurvival*

Variable	Survivors n = 36 Mean	Nonsurvivors n = 3 Mean
Age	46	56 (NS)
Tot. protein	7.1	7.6 (NS)
Tot. bilirubin	1.4	2.0 (NS)
Alk. phos.	180	136 (NS)
Sgot	60	76 (NS)

Non-alcoholic n = 39.

tively (operative mortality = 1.1%) and he (the patient) fulfilled the preoperative criteria for Child's Category A.

In Table 2 these same characteristics are compared for the alcoholic and nonalcoholic groups. The only significant differences were found in the serum enzyme determinations; alkaline phosphatase and glutamic oxalic transaminase activities. The degree of abnormality was greater in the nonalcoholic group for both enzyme functions despite the actuarial analysis of survival indicating a much greater probability of survival to six years for this group (Fig. 1). Further, comparison of these same preoperative characteristics for survivors versus nonsurvivors has failed to demonstrate any predictive differences (Table 3). This was true for the alcoholic group (Table 4) as well as for the nonalcoholic group (Table 5). The ten year difference in mean age between the survivors as compared to nonsurvivors in the nonalcoholic group is interesting and may have pertinence; however, the numbers are too small for statistical validation.

Histological evaluation of this small sample failed to uncover any significant differences between alcoholic and nonalcoholic liver biopsies based on the criteria listed previously. The average pathological score for the alcoholic patient was 4.2 and for the nonalcoholic patient, 4.3 (Tables 6 and 7). However, the biopsies from two patients, both of whom died of liver failure at one year postshunt, showed substantially greater disturbance of hepatic architecture and were graded 8 and 9 respectively (Table 8). This information is of sufficient interest to us such that we are evaluating all of the biopsies from the entire group in similar fashion in the hope of demonstrating the prognostic utility of liver biopsy for survival after distal splenorenal shunt.

TABLE 6. *Histological Grading Alcoholics, Living*

PT. #	A	B	C	D	E	Total
71-6112	0	1	1	1	0	3
73-7372	0	0	1	—	0	1
73-11892	0	0	2	2	1	5
75-10846	0	1	2	3	0	6
75-15729	0	0	3	2	1	6
n = 5						$\bar{x}_{alc} = 4.2$

TABLE 7. *Histological Grading Nonalcoholics, Living*

PT. #	A	B	C	D	E	Total
73-5796	0	0	2	2	0	4
73-15284	0	0	0	0	1	1
75-15461	0	0	1	2	0	3
75-2932	1	1	2	2	0	6
75-6502	0	0	2	2	0	4
75-10142	0	1	3	2	0	6
75-11814	1	0	2	3	0	6
n = 7						$\bar{x} = 4.3$

Discussion

The data presented in this report indicate a more favorable prognosis for longevity, at least to six years, in nonalcoholic compared to alcoholic patients after selective portasystemic shunt surgery (Fig. 1). Analysis of pertinent biochemical data does not demonstrate inferior liver function in the alcoholic group. In fact, the nonalcoholic patients presented with greater abnormalities in serum enzyme activities despite improved survival. Evaluation of a small sample (18%) has failed to show any significant differences in the severity of disturbances in hepatic histology between the two groups; however, it is possible that the sample size is too small to be significant. Nevertheless, it would appear that survival after distal splenorenal shunt cannot be related *completely* to the preoperative state of liver function or alterations in microanatomical structure. This is in sharp contrast to those findings reported after total portasystemic diversion. Therapeutic portacaval shunt has no significant effect on

TABLE 8. *Histological Grading, Nonsurvivors*

Classif/Number	Cause of Death	Total Grade
Alc/73-7373	Trauma	5
Nonalc/73-1075	Stroke	3
Nonalc/72-13728	Liver Failure	8
Nonalc/75-13758	Liver Failure	9

survival and this appears to be the same whether the cirrhotic process is alcohol related or not.[4] In at least two reports[2,6] survival is lower in nonalcoholic patients after total portal diversion.

In this study, the survival of alcoholic patients after selective shunting is the same as that reported for alcoholic patients after total portal diversion regardless of the fact of randomization or not.[4-6] In addition, the failure to survive does not appear to be related to preoperative liver function. In the light of these findings it seems reasonable to assume that continued exogenous toxicity due to alcohol abuse has an important role as a determinant of postoperative survival. Where this is not a factor, as in nonalcoholic cirrhotics, survival is appreciable greater despite initial inferior liver functional capacity and relatively similar disturbances in hepatic histology. It may be suggested further, that the failure to demonstrate improved survival after portacaval shunt in stable nonalcoholic cirrhotics may be due to the deleterious effects of this operation on liver function as caused by the acute diversion of all of the residual hepatic portal perfusion. To the extent that changes in the maximal rate of urea synthesis indicate such adverse effects, then this has been demonstrated to occur after total shunting.[7]

References

1. Cutler, S. J. and Ederer, F. E.: Maximum Utilization of the Life Table Method in Analyzing Survival. J. Chronic Dis., 8:699, 1958.
2. Foster, J. H., Ellison, L. H., Donovan, T. J., et al.: Quantity and Quality of Survival After Portasystemic Shunts. Am. J. Surg., 121:490, 1971.
3. Jackson, F. C., Perrin, E. B., Felix, W. R., et al.: A Clinical Investigation of the Portacaval Shunt. V Survival Analysis of the Therapeutic Operation. Ann. Surg., 174:672, 1971.
4. Kanel, G. C., Kaplan, M. M., Zawacki, J. K., et al.: Survival in Patients with Portnecrotic Cirrhosis and Laennec's Cirrhosis Undergoing Therapeutic Portacaval Shunt. Gastroenterology, 73:679, 1977.
5. Resnick, R. H., Iber, F. L., Ishihara, A. M., et al.: A Controlled Study of the Therapeutic Portacaval Shunt. Gastroenterology, 67:843, 1974.
6. Turcotte, J. G.: Portal Hypertension As I See It. *In* C. G. Child III (ed.) Portal Hypertension, Philadelphia, 1974, p. 109.
7. Warren, W. D., Rudman, D., Millikan, W., et al.: The Metabolic Basis of Portasystemic Encephalopathy and the Effect of Selective vs. Non-Selective Shunts. Ann. Surg., 180:573, 1974.
8. Zeppa, R., Hutson, D. G., Sr., Bergstresser, P. R., et al.: Survival After Distal Splenorenal Shunt. Surg. Gynecol. Obstet., 145:12, 1977.

DISCUSSION

DR. GEORGE JOHNSON, JR. (Chapel Hill, North Carolina): This paper presented by the group from Miami will be another milestone in the surgical attempt to control bleeding from esophageal varices. I remain a sceptic as to whether any operation can prolong the life of alcoholics. However, these data are very convincing for the nonalcoholic patient.

(Slide) Stimulated by the abstract, we reviewed our data for the ablative operation looking at the etiology of the cirrhosis. We did not have time to determine the histopathological and functional characteristics of these patients, nor to analyze the data by the life table method.

About 35% of our patients were nonalcoholics in this 24 year period. Unlike the data just reported, if there is any difference, the alcoholic patients who survived the operation lived longer. I suspect that this may be related to our frequent ability to stop the alcoholic from continued drinking.

(Slide) I would like to emphasize one point made by Dr. Zeppa. In the communication by Kanel, there is no difference in survival in the alcoholics and nonalcoholics after a portacaval shunt. The data from the Miami group showed that if alcohol is not a factor, the patient after a distal splenorenal shunt has a good chance for long-term survival. This is further evidence that after a portacaval shunt further liver damage inevitably occurs, and this limits the long-term survival, even in the nonalcoholic patient. If the patient continues to drink alcohol, neither operation is of much value in prolonging survival.

We have performed distal splenorenal shunts in ten patients, all of which had a good risk, without an in-hospital operative death in the past 18 months. We are pleased with the early results. Although three of the 22 mesocaval shunts we have created have thrombosed, the long-term results of the others appear to be satisfactory.

We were one among the many groups of investigators who spent years trying to predict the results of operations for portal hypertension by hemodynamics. We, as the others, were unsuccessful. Since I still believe this is a heterogeneous group of people, with different operations needed for the different people, we need a better way of typing these patients than the grading system that Child has presented to us. Thus, the greatest contribution of this paper may be the attempt to grade patients on the basis of the histopathological data. We will anxiously await further results of his experience with this.

Lately, we have seen a number of patients with primary biliary cirrhosis and portal hypertension, and wonder if patients with this disease have contributed to Dr. Zeppa's series. Although these patients have a guarded prognosis, the distal splenorenal shunt would seem to be the operation of choice.

DR. HUNTER H. MCGUIRE, JR. (Richmond, Virginia): I'd like to say a word about the distal splenorenal shunt from the perspective of a beginner, which is where I think most of us in the audience probably are. We all have one very big disadvantage. Unlike Drs. Warren and Zeppa, most of us have not got so many good patients.

Dr. Zeppa has reported that he has found 66% of his patients are satisfactory candidates for distal shunts. On my service, only 20%, or five cases per year, are free of ascites. In a setting like this, we beginners must ask ourselves two questions. The first is: Can we do any occasional distal splenorenal shunt safely?

The hardest part of the procedure, in my experience, is not the technique, but compelling anesthetists and house staff to withhold intravenous saline. My three patients who got no saline have done perfectly, and one who got 13 g of salt in the operating room and 7 g a day postop died in hepatorenal syndrome. Bob Zeppa has clearly warned us against this practice, and its a warning that we must very carefully repeat to anyone who occasionally helps us in taking care of these patients.

The second question we have to ask ourselves is: Will any shunt prove cost-effective in the care of the alcoholic patients? On my service, 98% of bleeding varices are alcoholics. I think that probably is applicable to most of us who haven't developed a special referring practice.

It's really not certain, I don't think, that any portal systemic shunt is worthwhile in alcoholics, but common sense dictates that the

Warren shunt, which makes a patient no worse, and effectively prevents one major mode of death, has got to add to the life of the group as a whole. Therefore, I feel that we are obliged to offer the Warren shunt to nonascitic alcoholics, even if our opportunities to do so are rare.

DR. W. DEAN WARREN (Atlanta, Georgia): I simply want to rise to say that this is not the Warren shunt. It's the selective distal splenorenal shunt we worked out with a team in Miami. I congratulate Dr. Zeppa on achieving, in my opinion, the finest statistics in this field in the world. I know of none who can equal the results he has just presented.

One point of importance, if you noticed, is their judicious choice of time of operation; they don't operate on the man just because he comes in bleeding and there is available operating time on Thursday! You treat the patients, get them in the best possible condition, and then do the best operation.

DR. ROBERT ZEPPA (Closing discussion): I'd like to show just one slide, if I may, (slide) which illustrates—and perhaps this kind of illustration is not quite accurate; it may be a little bit invidious. But it does show what Dr. Johnson put up on the screen; however, plotted in the same actuarial analysis against other data.

These are graphs of the survivals of nonalcoholic patients from the series that I mentioned. This one is the one of Kanel, the only one where an actuarial approach was used similar to ours. These have been corrected for the mortalities indicated up at the top. There is a significant difference between the survival of patients with postnecrotic cirrhosis after portacaval shunt as compared to the distal splenorenal shunt.

With respect to the comments that Dr. Johnson has made about the alcoholics—do they stop drinking?—we think we may have a few in the series who have stopped, but I would not like to stake next month's salary check on it. However, they are alive, and they tell me they have stopped drinking. Their liver function is stable.

What is very important in this is that we have been collecting the death certificates, inaccurate though they may be, on all of our patients, as we follow them with our nurse clinicians chasing them; and by far the most common mechanism of dying after the distal splenorenal shunt if you are an alcoholic is trauma—stabbings, auto accidents, and that kind of business.

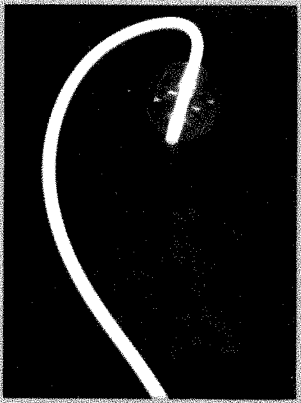
So I don't know how to attack the question that was given me both by Dr. McGuire and by Dr. Johnson: What do we do for alcoholics? I like Dr. McGuire's remarks about applying an operation that, in general, will not give them increased liver failure—and hope for the best.

PROBLEM: Reflux and Migration of Embolic Agents

SOLUTION: MEDI-TECH Occlusion Balloon Catheters

REF: Greenfield, A.J.; Transcatheter Embolization: Complications and Prevention With Balloon Catheters. PROGRAM OF THE AMERICAN ROENTGEN RAY SOCIETY: Seventy-eighth Annual Meeting, September 26-30, 1977, Boston, Mass.

Arteriogram performed with balloon inflated prior to embolization



Medi-Tech Occlusion Balloon Catheter OB/7/2/65 (also used in X-Ray at left)

When carrying out therapeutic embolization, the risk that embolic agents will be carried to non-intended locations should be considered.

REF: Woodside, J.; Schwarz, H.; Bergreen, P.: Peripheral Embolization Complicating Bilateral Renal Infarction With Gelfoam. American Journal of Roentgenology: Vol. 126: 1033-1034, 1976.

Gang, D.L.; Dole, K.R.; Adelman, L.S.: Spinal Cord Infarction Following Therapeutic Renal Artery Embolization. JAMA: VOL. 237, No. 26, June, 1977.

Bradley, E.L.; Goldman, M.L.: Gastric Infarction After Therapeutic Embolization. SURGERY: Vol. 79, No. 4, April, 1976.

With the development of the MEDI-TECH Occlusion Balloon Catheters this risk has been significantly reduced.

MEDI-TECH offers the only balloon catheter available today with a polyethylene catheter body. Unlike polyvinyl chloride (PVC) which softens at body temperature, polyethylene retains its torque and holds pre-set curves. This enables selective placement of the balloon either with or against the blood flow.

The smooth tip profile and large I.D. (.038" in the 7F) allow percutaneous introduction by Seldinger Technique over a .035" guide wire.

(For more information fill out the coupon below and mail, or call Toll Free 800-225-3238).
In Massachusetts 617-923-1720.

CATHETERS AVAILABLE

Catalog Number	French	Lumens	Balloon Dia. (mm)	Tip I.D. (.000")	Usable Length (cm)
OB/7/2/65	7	2	12	38	65
OB/7/2/100	7	2	12	38	100
OB/5/2/65	5	2	8.5	27	65
OB/5/2/100	5	2	8.5	27	100

MEDI-TECH
Div. of Cooper Scientific Corporation
372 Main Street • Watertown, Massachusetts 02172

☐ I'd like more information sent
☐ I'd like a representative to call

Name ______ Dept. ______
Hosp. ______
Address ______
City ______ State ______ Zip ______
Phone ______ ( ) Area Code

If Saving Lives is Your Business . . .

You should know about life-saving MAST®

MAST is the original Medical Anti-Shock Trouser* manufactured by David Clark Company.

MAST can be positioned and applied in 60 seconds.

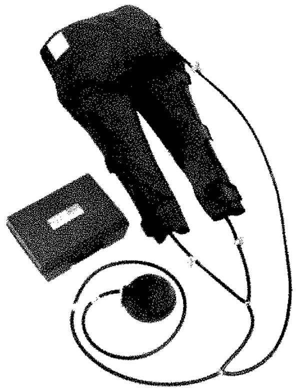
MAST produces rapid autotransfusion for control or reversal of shock,** and can check trauma from application right up to surgery.

MAST exclusive automatic relief valves prevent overpressurization. Eliminates necessity of constantly monitoring pressure gauges.

MAST Velcro closures provide easy operation and a snug fit for better pressure stability and patient comfort.

MAST can be counted on to continue to work satisfactorily in extreme heat and cold.

If you care about good Emergency Care you should know more about life-saving MAST.
Distributed nationwide. Send for FREE brochure and name of local emergency equipment suppliers.



*Patent No. 3,933, 150
**Documented Case Histories available upon request.

David Clark COMPANY
INCORPORATED
365 Franklin St., Worcester, MA 01604 (617) 756-6216

Regional Offices: Dallas, TX (214) 321-3323; Dayton, OH (513) 433-0033; Georgetown, SC (803) 546-2223; Los Angeles, CA (213) 776-4571, Philadelphia, PA (215) 878-1905.
Distributed in Canada by Levitt Safety Ltd.

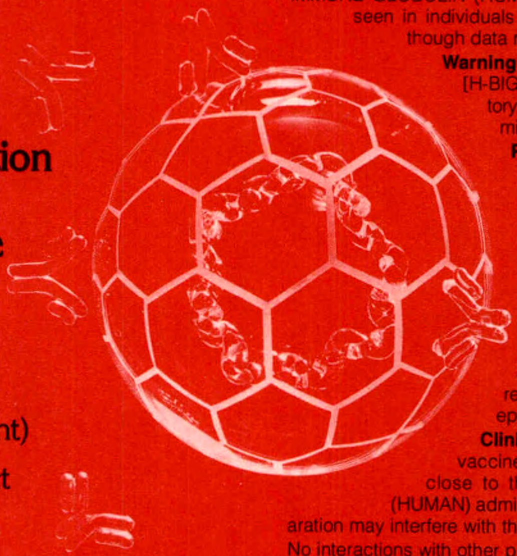
Are you at high risk for Hepatitis B?

Now available for post-exposure prophylaxis

H-BIG®

HEPATITIS B IMMUNE GLOBULIN (HUMAN)

from ABBOTT
Scientific Products Division



Provides short-term protection for individuals accidentally exposed to material reactive for HB$_s$Ag by:

- parenteral means (e.g., accidental needle-stick)
- oral means (e.g., pipetting accident)
- direct mucous membrane contact (e.g., accidental splash)

Who's at risk?

- Staff and patients in hemodialysis units, oncology wards
- Operating room personnel
- Technologists in private and hospital laboratories, blood banks
- Physicians—especially surgeons
- Dentists—especially oral surgeons
- Staff and patients in long-term institutions
- Chronic users of injection therapy
- Other hospital staff

ABBOTT Scientific Products Division
Abbott Laboratories
820 Mission Street, South Pasadena, California 91030

Brief Summary

Clinical Pharmacology/Biological Activity: HEPATITIS B IMMUNE GLOBULIN (HUMAN) provides passive immunization for individuals exposed to the hepatitis B virus (HBV) as evidenced by a reduction in the attack rate of hepatitis B following its use. The administration of the usual recommended dose of this immune globulin generally results in a detectable level of circulating anti-HB$_s$ which persists for approximately two months or longer. Cases of type B hepatitis are rarely seen following exposure to HBV in persons with pre-existing anti-HB$_s$. No confirmed instance of transmission of hepatitis B has been associated with this product.

Indications: HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®] is indicated for post-exposure prophylaxis following either parenteral exposure, e.g., by accidental "needle-stick," or direct mucous membrane contact, (e.g., accidental splash), or oral ingestion, (e.g., pipetting accident) involving HB$_s$Ag positive materials such as blood, plasma or serum.

Use of HEPATITIS B IMMUNE GLOBULIN (HUMAN) in other situations has been and continues to be evaluated, but there are not sufficient data at present on effectiveness, dosage and schedule for any other uses to be included as definite indications. There is currently some controversy over whether immune globulin containing a low or a high anti-HB$_s$ titer is preferable in these other situations.

Contraindications: There are no specific contraindications for HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®]. No adverse reactions have been seen in individuals with pre-existing hepatitis B surface antigen although data regarding this occurrence are limited.

Warning: HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®] should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immune globulin preparations.

Precautions: *GENERAL:* HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®] should not be administered intravenously because of the potential for serious reactions. Injections should be made intramuscularly, and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel.

CLINICAL AND LABORATORY TESTS: None required.

SPECIAL INSTRUCTIONS: Although systemic reactions to immune globulin preparations are rare, epinephrine should be available.

Clinically Significant Product Interactions: Live virus vaccines such as measles vaccine should not be given close to the time of HEPATITIS B IMMUNE GLOBULIN (HUMAN) administration because antibodies in the globulin preparation may interfere with the immune response to the vaccination.

No interactions with other products are known.

Pregnancy: No studies have been conducted in pregnant patients. Clinical experience with other immunoglobulin preparations administered during pregnancy suggests that there are no known adverse effects on the fetus from immune globulins per se, but there are no reported studies indicating whether or not such adverse effects occur.

Adverse Reactions: Local pain and tenderness at the injection site, and urticaria and angioedema may occur; anaphylactic reactions, although rare, have been reported following the injection of human immune globulin preparations.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

We have prepared a package of informational materials to acquaint you and your staff with HEPATITIS B IMMUNE GLOBULIN (HUMAN). Return this coupon to receive your copy of ASPD's "Seminar in Print."

Send to:
ABBOTT Scientific Products Division
820 Mission Street
South Pasadena, California 91030

☐ Have representative contact me
☐ Send order information

Name ______________________________

Position ______________________________

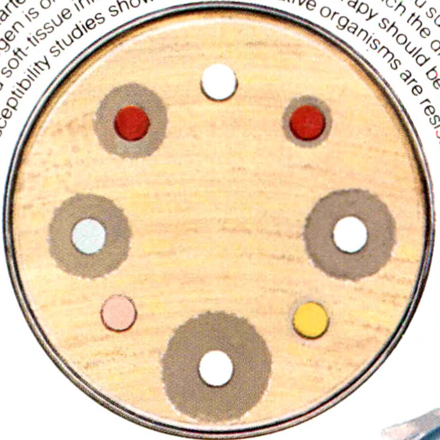
Institution ______________________________

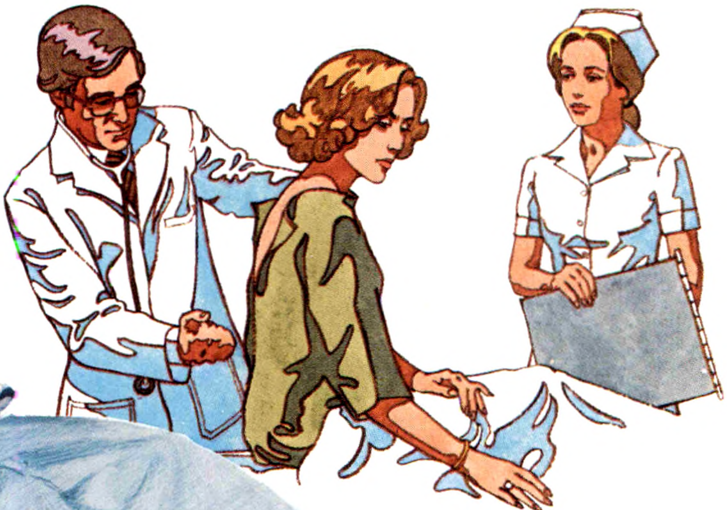
Address ______________________________

City ______________ State ______________ Zip ______________

AS-5

Appropriate cultures should be taken, but Keflin® (cephalothin sodium, Lilly) may be started before susceptibility results are obtained if you suspect the causative pathogen is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections.* Other antibiotic therapy should be instituted if susceptibility studies show that the causative organisms are resistant.

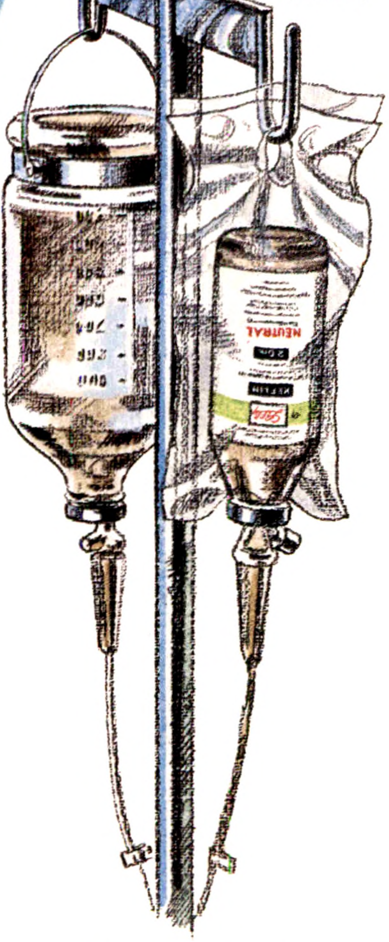


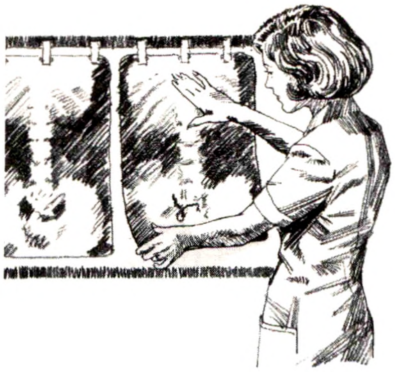


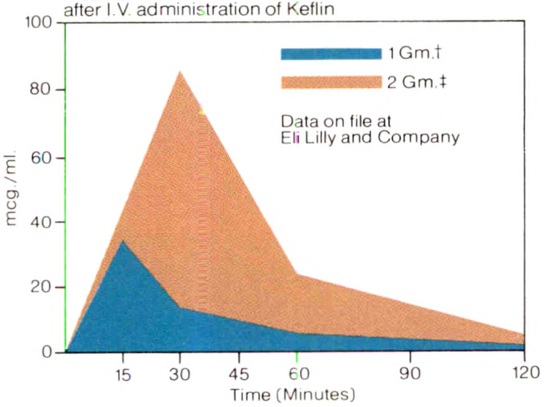
In the immunosuppressed patient, usual clinical signs and symptoms of infection may be missing or not clear. Hence, diagnosis and initiation of proper therapy become most urgent.

An initial loading dose of 1 to 2 Gm. of Keflin may be given regardless of the patient's renal status. Patients with impaired renal function should be placed on a reduced dosage schedule. Usual doses in such individuals may result in excessive serum concentrations.

Keflin may be administered I.V. or I.P. in dosages as high as 12 Gm. per day (in life-threatening infections).







Mean serum concentrations after I.V. administration of Keflin

† Administered to six patients by rapid I.V. infusion.

‡ Administered to ten patients over a thirty-minute period.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

Please see opposite page for summary of prescribing information.

In serious skin and soft-tissue infections*

OFTEN USEFUL WHEN MOST NEEDED

As you know, skin and soft-tissue infections,* including peritonitis, may progress with alarming rapidity in patients with impaired host defenses...even to the point of becoming irreversible. Keflin can often be useful before the infection becomes irreversible...exactly when it is most needed.

Eleven years after its introduction, Keflin continues to be effective against most strains of gram-positive and gram-negative organisms commonly implicated in serious skin and soft-tissue infections.* Therefore, when you suspect that the pathogen involved is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections,* you may begin therapy with Keflin even while results of susceptibility studies are pending...and thus save precious hours for the patient. Keflin may be administered to infants and to patients with reduced renal function.

Keflin should be given cautiously to penicillin-sensitive patients.

It is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

* Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Keflin® 2 Gm.† in 100-ml. ampoule

cephalothin sodium

Neutral

for Injection

†Equivalent to cephalothin

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin® (cephalothin sodium, Lilly), Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy – Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [111475S]

Additional information available to the profession on request

Lilly

Eli Lilly and Company

"Current abstracts are amplified and illuminated by comments of the members of the Editorial Board, based on their own clinical experiences as well as those of other recognized authorities" . . . just one of the reasons why Lippincott's

Current Surgery *Formerly REVIEW OF SURGERY*

Editor: Lloyd M. Nyhus, M.D.

Associate Editors: Robert E. Condon, M.D.,
W. G. Schenk, Jr., M.D., Seymour Schwartz, M.D.

helps Resident (special rate only $15.00) and Veteran Surgeon alike to keep up with current progress, trends, and attitudes in all branches of surgery and the surgical specialties.

A true saver of precious reading time—from its detailed Contents Pages to its meaty reviews, and abstracts especially classified for reader convenience—a typical issue includes:

- Focus—several Reviews of timely or other special significance
- An original Report of major importance
- Twenty or more Abstracts with Commentary (and oft-times, rebuttal)
- Residents Corner—comprising Brief (1 to 3-page) Reports and Investigations
- In-depth Reviews of Current Books in Surgery

TO PUT THE BIMONTHLY CURRENT SURGERY AT YOUR FINGERTIPS NOW,

SUBSCRIBE TODAY . . .

J. B. LIPPINCOTT COMPANY, East Washington Square, Philadelphia, Pa. 19105 AS 5/78

Please enter my subscription to CURRENT SURGERY for 1 year (6 issues), at ☐ **$19** (U.S.); ☐ **$23** (all other countries); Resident Rate ☐ **$15** (U.S. only; also note "year" of residency and Specialty ____________).

PLEASE PRINT

Name ____________

Address ____________

City/State/Zip ____________

☐ Payment Enclosed.

☐ Charge my account.

My Specialty is:

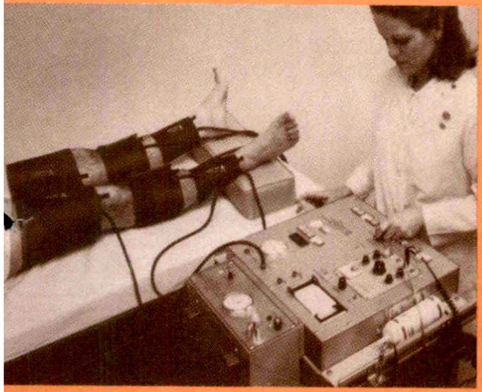
____

The Lsi NON-INVASIVE Clinical Vascular Laboratory

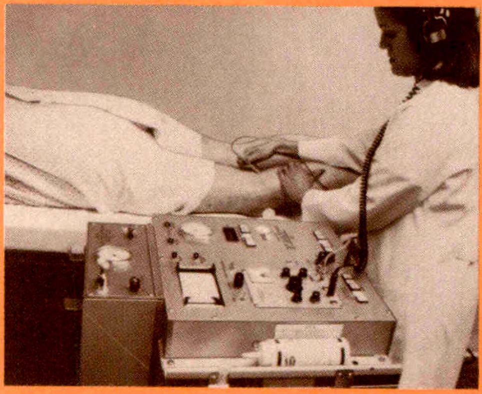
PULSE VOLUME RECORDER (PVR®)*

An Extensively Documented Clinical Procedure for the Quantitative Evaluation of Peripheral Vascular Disease: Arterial—Venous—Cerebral Vascular

Arterial

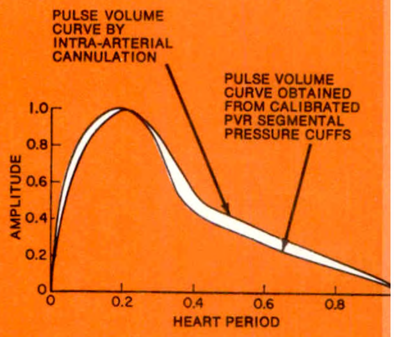


Total Segmental Perfusion (primary vessel plus collaterals) is accurately documented at the thigh-calf-ankle-metatarsal level and digits.



The built-in Doppler facilitates the measurement of pressures along the arterial tree.

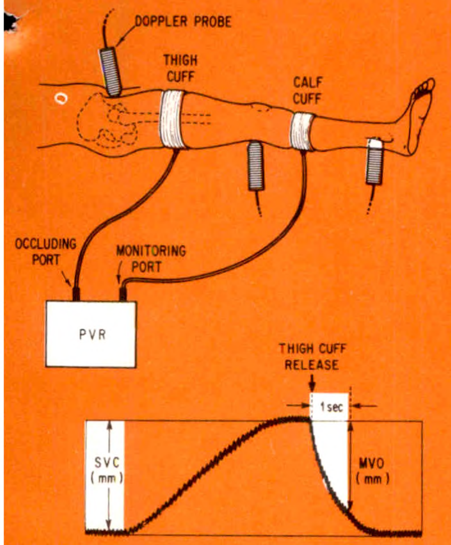
The COMBINED information of segmental PVR recordings and systolic pressure gradient establishes a clinically accurate picture of segmental perfusion.



Comparison of pressure contours obtained with the PVR and direct cannulation of the common femoral artery.

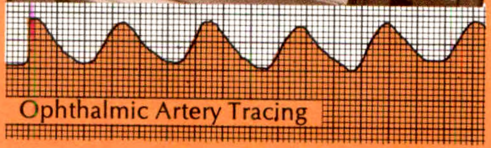
EXCELLENT LONG-TERM REPRODUCIBILITY AND CALIBRATED ACCURACY BY QUANTITATIVE SEGMENTAL CUFF TECHNIQUE

Venous



A 15-point scale provides quantitative criteria for the identification of increased deep venous resistance.

Cerebral



Ophthalmic Artery Tracing

Ophthalmic artery pressure is read directly on the OPG Attachment of the PVR for the evaluation of collateral circulation to each eye, and its respective cerebral hemisphere.

The CLINICAL PROCEDURES for the Evaluation of Peripheral Vascular Disease based on the Pulse Volume Recorder (PVR®) described here, have been qualified for reimbursement for In- and Out-Patients under:

- Various non-profit hospital and medical-surgical service plans
- Medicare
- Veterans Benefits
- Commercial Insurance Companies

For In-Hospital use or Office-Based Practice.

References, bibliography, and details on request.

Life Sciences Inc.
270 Greenwich Avenue
Greenwich, Connecticut 06830 U.S.A.
Tel. 203 869-2011

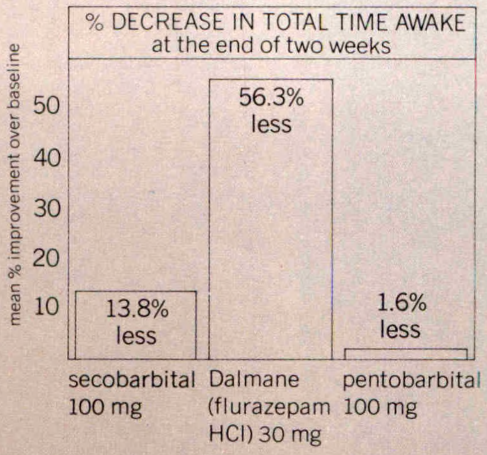
14-night sleep laboratory studies prove:[1-3]

BARBITURATES DO NOT MATCH THE EFFECTIVENESS OF DALMANE (flurazepam HCl)

Consider these differences:

In sleep laboratory studies, barbiturates have not been able to match the effectiveness of Dalmane (flurazepam HCl) over time.

Dalmane 30 mg maintained its efficacy in inducing and maintaining sleep over 14 consecutive nights in the sleep laboratory.[1] In a study using the same protocol, secobarbital 100 mg lost most of its effectiveness within two weeks.[2] And in another study,[3] Dalmane 30 mg remained effective for 28 consecutive nights in chronic insomniacs, whereas pentobarbital was found to be effective only with short-term use. Although seldom necessary, prolonged administration of Dalmane should be monitored with periodic blood counts and liver and kidney function tests.



For your patients, there are important safety advantages of Dalmane (flurazepam HCl)

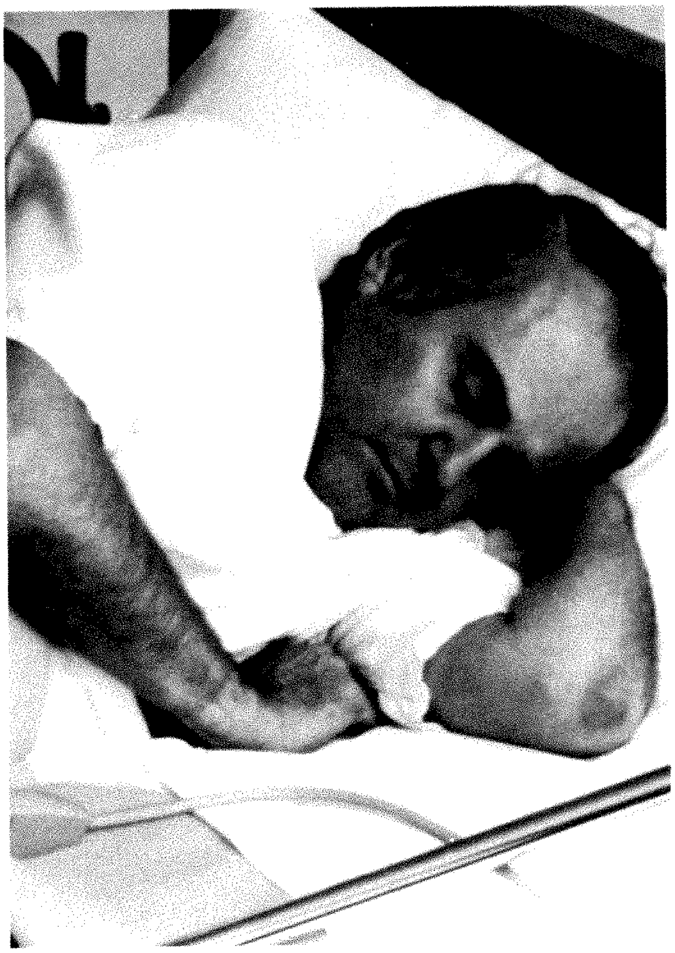
☐ Generally well tolerated, Dalmane seldom causes morning "hang-over."
☐ Unlike barbiturates, which have been reported to decrease the response to coumarin anticoagulants,[4] Dalmane may be used in patients on chronic warfarin therapy; no unacceptable fluctuation in prothrombin time has been reported. In two controlled studies,[5,6] in which therapeutic doses of Dalmane or matching placebo were administered for 28 consecutive days to outpatients receiving chronic warfarin therapy, Dalmane was found not to be an inducer of hepatic microsomal enzymes which metabolize warfarin. There was also no clear-cut evidence, in these studies, of potentiation of the anticoagulation effect of warfarin by Dalmane (flurazepam HCl).
☐ Recent studies show that Dalmane and its known metabolites do not interfere chemically with many commonly ordered laboratory tests.[7-9] Alterations have been reported due to pharmacologic effects (see Adverse Reactions section of product information).

ANOTHER
DALMANE®
(flurazepam HCl) Ⓒ IV
DIFFERENCE:

Superiority over barbiturates and no need to repeat dose

ROCHE

Please see following page for a summary of product information.



UNSURPASSED RECORD
OF SAFETY AND EFFICACY

DALMANE®
(flurazepam HCl)

30-MG AND 15-MG CAPSULES

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:
Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, limit initial dosage to 15 mg to preclude oversedation, dizziness and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

REFERENCES: 1. Kales A, *et al*: *Arch Gen Psychiatry 23*:226-232, Sep 1970. 2. Kales A, *et al*: *Clin Pharmacol Ther 20*:541-545, Nov 1976. 3. Kales A, *et al*: *Clin Pharmacol Ther 18*:356-363, Sep 1975. 4. Hansten PD: *Drug Interactions*, 3rd edition. Philadelphia, Lea & Febiger, 1975. 5. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641. 6. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. 7. Kaplan SA, *et al*: *J Pharm Sci 62*:1932-1935, 1973. 8. Moore JD, Weissman L: *J Clin Pharmacol 16*:241-244, May-Jun 1976. 9. Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

ROCHE

ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

Results of Interposition "H" Grafts for Portal Hypertension

BERNARD W. THOMPSON, M.D., F.A.C.S.,* ROBERT E. CASALI, M.D.,† RAYMOND C. READ, M.D., F.A.C.S.,‡
GILBERT S. CAMPBELL, M.D., F.A.C.S.§

From the Department of Surgery,
University of Arkansas for Medical Science,
Little Rock, Arkansas

During the past nine years, 54 patients underwent interposition graft shunting for variceal bleeding in 48 and intractable ascites in six, either electively (35 instances) or as an emergency (13 instances). Autogenous jugular was used in 41 instances, homologous vena cava in nine and Dacron® in five. The interposition graft was placed between superior mesenteric vein and vena cava in 36 instances and the portal vein and vena cava in 19. Using Child's Clinical Classification 44 were Class C and 10 Class B. There were six (11%) operative deaths with one (2.4%) in the elective and five (38%) in the emergency group. Encephalopathy was seen in 4 (10%) of those surviving more than one year. Two Dacron and two homografts thrombosed. Eight of the autografts were patent at autopsy, 18 on angiography and 15 assumed to be patent because patients were asymptomatic. Only one of 12 late deaths was related to graft failure. Apparently the operation controls ascites and the autogenous jugular vein is the ideal material. Interposition "H" grafting is a simple safe procedure that can be used for portal decompression in patients with bleeding varices.

AN ANASTOMOSIS BETWEEN the protal and systemic venous circulations was first performed by Eck in 1877.[5] He suggested that this technic might be useful in treating patients with ascites. The operation was attempted by a number of surgeons, mainly in Europe, but generally with poor results. The first successful series of portacaval shunts were described by Blakemore and Lord[2] and Whipple[43] in 1945. Unfortunately, surgical decompression by direct portacaval anastomosis is frequently difficult to accomplish because of congestion of the liver with hypertrophy of its caudate lobe, arteriovenous fistulas in the retroperitoneal area, enlarged lymphatics and edema about the porta hepatis or, especially in children, thrombosis of the portal vein. Transection of the inferior vena cava with suturing of the orifice of the proximal segment into the side of the superior mesenteric vein was introduced by Valdoni[40] in 1954. It was later popularized by Marion[24] and Clatworthy,[7] as another site for portal decompression.

Although the mesocaval shunt is almost uniformly applicable, as thrombosis of the superior mesenteric vein is rare, Gliedman and Margulies[16] as well as Voorhees and Blakemore[41] have noted marked swelling of the lower extremities, especially in the adult alcoholic with hypoproteinemia. Therefore, in an attempt to leave the venous return from the lower half of the body unimpaired as well as to simplify the operative procedure and perhaps reduce its mortality and morbidity especially in alcoholics whose variceal bleeding does not respond to non operative management, we adopted in 1968 the routine use of the Interposition "H" Graft. Interposition of an autogenous vein between the portal and systemic venous system was first carried out in 1951 by Reynolds and Southwick.[32] Isolated cases were reported in the 1960's using prosthetic material, by Yeoh and Eiseman,[44] Foster et al.,[13] Preston and Trippel[28] and Nabseth and associates.[26] We first used venous homografts to bridge the gap between the two circulations.[31] Lord et al.,[19,20] Drapanas,[9,10] and Giles and associates[15] advised the use of prosthetic materials. More recently Thompson and Read[37–39] as well as Stipa et al.[35,36] have employed autogenous jugular vein. Dale and Scott[8] and Betancourt and associates[1] have shown in experimental animals that autogenous grafts evoke the least perivascular reaction and is the most satisfactory material for venous grafting when compared to homograft and prosthetic material.

Materials and Methods

During the past nine years, 55 interposition "H" grafts between the portal and systemic venous circula-

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests to B. W. Thompson, M.D., F.A.C.S., Assistant Chief, Department of Surgery, Veterans Administration Hospital 300 East Roosevelt Road, Little Rock, Arkansas 72206.

* Assistant Chief, Department of Surgery, Veterans Administration Hospital, Professor, Department of Surgery, University of Arkansas for Medical Science, Little Rock, Arkansas.

† Assistant Professor of Surgery, University of Arkansas for Medical Science, Little Rock, Arkansas.

‡ Chief, Department of Surgery, Veterans Administration Hospital, Professor, Department of Surgery, University of Arkansas for Medical Science, Little Rock, Arkansas.

§ Professor and Chairman, Department of Surgery, University of Arkansas for Medical Science, Little Rock, Arkansas.

0003-4932-78-0500-0515-0085 © J. B. Lippincott Company

tions have been performed on 54 patients. Forty-six were white and eight black. There were 48 men and six women whose age ranged from 21 to 70 years with an average of 49. In 48 patients, cirrhosis was secondary to alcoholism while in six it was postnecrotic. All but six of the 54 patients had had up to seven episodes of massive hemorrhage and received from 1,500 to 35,000 ml of blood prior to operation. The six exceptions were patients operated on for ascites intractable to diuretics and salt restriction. Thirteen of the 49 shunts were performed during an acute episode, while the other 36 were delayed two to six weeks. Fifty patients had clinical evidence of ascites prior to surgery.

Results of liver function studies were abnormal in all. Total serum protein levels ranged from 3.4 to 7.8 g/100 ml while the serum albumin levels varied from 1.2 to 3.7 g/100 ml. Sulfobromophthalein retention measured 10–45%. The serum bilirubin level was within normal limits in three patients, while it varied from 2.0 to 34.0 mg/100 ml at the time of operation in the others. With the exception of the six patients operated on for ascites, all patients showed esophageal varices on either esophagoscopy, portal venous angiography or barium studies. Using Child's method of clinical evaluation,[6] we placed 44 patients in Class C and ten in Class B.

Operative Technique

An incision is made, on the right side of the neck parallel of the anterior border of the sternocleidomastoid muscle, extending from the base of the skull to the suprasternal notch. The internal jugular vein is identified in the carotid sheath and dissected free from the vagus nerve and common carotid artery. The vein is then ligated at each end and removed for use as an autograft. The vein varied from 7.5 to 10.0 cm in length with a diameter of 1.0–2.0 cm. Autogenous jugular vein was used on 41 occasions, homologous vena cava was employed earlier in nine and Dacron® in five of the emergencies.

In 36 instances, the interposition graft was placed between the superior mesenteric vein and the inferior vena cava, in 19 it was situated between the portal vein and inferior vena cava.

For mesocaval interposition, a long midline incision is made. The transverse mesocolon is elevated superiorly and the small bowel retracted downward. Portal pressure is measured in a small venous tributory of the midcolic vein dissected out in the transverse mesocolon. The superior mesenteric vein is then identified at the right border of the mesentery adjacent to the pulsation of the artery and examined for patency. The inferior vena cava is then identified by retracting the small bowel to the right and superiorly, exposing the cava at the brim of the pelvis just after the confluence of the iliac veins. The anterior surface is cleaned for a distance of 2–3 cm so that a partially occluding clamp can be applied after systemic heparinization. Heparin sodium 120U/Kg is given intravenously and activated clotting times monitored at 20 minute intervals. We attempt to prolong the activated clotting time 200% during vascular anastomosis. The activated clotting time is returned to normal following completion of the anastomosis by giving intravenous protamine sulfate in 20 mg increments. After the partially occluding clamp is applied to the vena cava, an ellipse of this vessel is excised the autograft is then sutured to the vena cava with a continuous 5-0 prosthetic monofilament material. The peritoneum over the superior mesenteric vein is opened and the vein is isolated dissecting out the confluence of the mid colic and inferior pancreatic branches above and below the right colic tributary. The dissection is limited superiorly by the pancreas, which should not be injured, and inferiorly by the right colic artery crossing anteriorly. There is some variation in the length of the vein but it has always been adequate for anastomosis. A finger is then passed through the right colic mesentery inferior to the transverse portion of the duodenum to join the two dissections. The graft is allowed to fill with blood under pressure which rotates it slightly and prevents kinking as it passes caudal to the duodenum to enter the superior mesenteric vein. A small ellipse of the superior mesenteric vein is removed posterolaterally after blood flow has been controlled by vascular clamps. The posterior row of the anastomosis is completed with 5-0 prosthetic material. After removal of the clamp on the graft to assure patency, the anterior anastomosis is completed with a continuous suture (Fig. 1).

For portacaval interposition the patient is placed in the left lateral position with the kidney rest elevated. A long skin incision is then made starting just below the xiphoid and parallel to the costal margin all the way around the flank to the transverse process of the second lumbar vertebra. The subcutaneous tissues and underlying muscles are divided transversely. Any ascitic fluid is then aspirated. The peritoneum over the porta hepatis is incised to expose the right lateral portion of the portal vein. Pressure in the portal vein is measured by direct insertion of a needle. After giving the sodium heparin 120 U/kg, a Satinsky vascular clamp is applied to the portal vein and an ellipse of this vessel is removed. The autogenous jugular vein is sutured to this defect in the portal vein with an anterior and posterior whipping stitch of 5-0 monofilament prosthetic suture. The occluding clamp is then removed. The posterior peritoneum is then incised over the anteriomedial wall of the inferior vena cava for a distance of 2–3 cm.

A partially occluding clamp is applied to this vessel and a button of tissue of removed from the vena cava. The posterior anastomosis is made with a continuous 5-0 monofilament prosthetic material. The clamp on the graft is removed to assure patency and the anterior anastomosis is then completed. Post-shunt pressures are then taken in both the portal and caval systems. When any doubt exists about shunt flow an angiographic study is performed before abdominal closure (Fig. 2).

Results

Six of the 54 patients died within one month of the their interposition graft. Five of these deaths were in the 13 patients operated on as emergencies while bleeding. Four seemed to do well after surgery only to develop deepening icterus, ascites and somnolence. They died on the eleventh, fourteenth, twenty-first and twenty-seventh days. Two others died on the sixth and tenth postoperative days. Both of these had markedly increased pressure in their vena cavas at the time of surgery (240 and 400 mm H_2O). After their shunts were completed the pressure in the portal system fell only minimally. Both showed progressive liver failure, ascites and decreasing urinary output despite large amounts of fluid and albumin replacement. At autopsy there was almost complete occlusion of the inferior vena cava by an hypertrophied caudate lobe in both. In one the Dacron mesocaval graft was found to be thrombosed.

Three additional patients have had thrombosis of their interposition grafts. Two patients who had "H" grafts tunneled between the duodenum and pancreas developed hematemesis six and nine months after surgery. The first patient, at six months was found to have a splenic pulp pressure of 35 cm of saline and occlusion of the graft on splenoportography. At a second operation the thrombosed homograft was removed. It was occluded by a swollen pancreas and a second homograft was inserted as an interposition "H" graft caudal to the duodenum. He is asymptomatic 98 months after surgery. The second patient refused further surgery only to return to the hospital six weeks later and died as a result of variceal hemorrhage. At autopsy there was evidence of pancreatitis with resulting fibrosis occluding the homograft. The third patient had an uneventful postoperative course following a Dacron interposition portacaval procedure. He returned six months later with ascites, progressive icterus and massive upper gastrointestinal tract bleeding. He died shortly after admission. His graft was found to be thrombosed at autopsy.

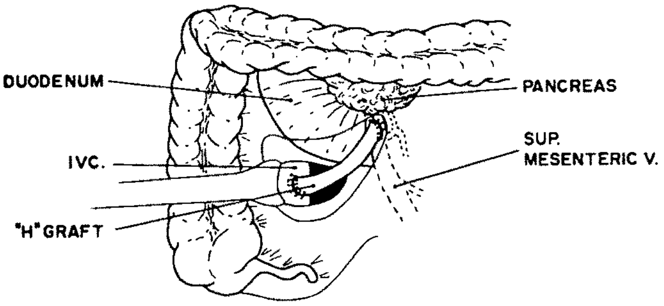


FIG. 1. Interposition autogenous jugular vein inserted between the superior mesenteric vein and inferior vena cava.

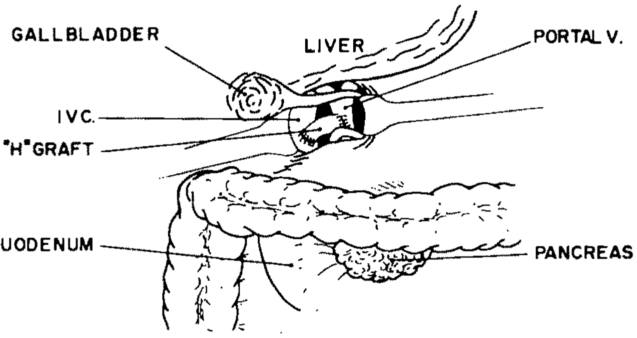


FIG. 2. Autogenous jugular vein inserted as an "H" graft between the portal vein and inferior vena cava.

Three patients developed hepatomas at four, six and 18 months after operation. Two had cirrhosis secondary to alcoholism and in the third cirrhosis was secondary to hepatitis. All three recovered uneventfully from their operations only to return later with progressive icterus, ascites and terminally, somnolence, generalized bleeding, coma and death. The interposition grafts were patent at autopsy in all three.

Seven patients died from six to 38 months after interposition grafting. They continued heavy alcohol intake. Two died at 30 and 34 months from aspiration pneumonia. Three other patients developed hepatorenal syndrome and died at 16, 22 and 38 months; complete destruction of the liver apparently due to continued alcoholism was found at autopsy. Two other patients died from complications of duodenal ulcer. The first died six months after "H" grafting from peritonitis secondary to an acute duodenal ulcer perforation. He had perforated his ulcer at home and was not seen by a physician for some 96 hours when he was terminal. The second patient developed massive gastrointestinal hemorrhage while being treated for acute alcoholism. He died without surgical consultation 32 months after shunting and at autopsy was found to have a large duodenal ulcer from which he had bled. The grafts were patent in all seven of these patients.

Six of the 46 long-term survivors (6–104 months) have had melena or hematemesis since surgery. Gastrointestinal tract barium studies as well as endoscopic examination have demonstrated duodenal ulcer in four patients and hemorrhagic gastritis in two. Splenoportography by direct splenic injection and more recently using delayed films after selective splenic artery injection, have shown the shunts are patent in the 18 visualized. In all 30 survivors operated on for varices, these have decreased in size as determined by barium studies.

Four patients have been readmitted for mental confusion, somnolence or coma associated with elevated serum ammonia levels. Three of these have had a single episode of encephalopathy; one at two months and two at three months following the shunt procedure. All three were treated with protein restriction and lactulose 30 ml three times daily and are doing well nine, 12 and 16 months later. The fourth patient has had two episodes of encephalopathy two and four months following his shunting procedure. He was initially felt to have cirrhosis secondary to hepatitis. He continues to have a positive HAA and is felt to have chronic active hepatitis and in addition to protein restriction is being given azothioprine, prednisone and lactulose.

Immediately after operation there is frequently a transient increase in ascites and icterus. If severe enough this can lead to death as indicated previously. We have had an example of this in a long term survivor who developed increasing ascites, deepening icterus and decreasing urinary output after mesocaval shunt. His liver function studies finally improved after four months of intensive fluid therapy.

All six patients operated on for intractable ascites are now working and are free of intra-abdominal fluid. Their ascites is easily controlled by either salt restriction or mild diuretics. No complications have been associated with removal of the jugular vein and the scar has not been disfiguring.

Discussion

Interposition grafting for portal hypertension has been performed for almost 30 years.[32] Considerable experience has been gained using autografts,[36-39] homografts[31] and prosthetic material.[9-11,15,19 20] There is increasing evidence that, contrary to previous opinion,[23,34] this procedure is not just a variant of side to side portacaval anastomosis. It appears that, different to the latter, some portal flow to the liver is maintained as shown previously by angiographic studies by Read et al.[31] and in 44% of 80 patients by Drapanas.[10] More recently Harmon et al.,[17] using radioactive microspheres in experimental animals, have shown that after side-to-side portacaval shunt no blood goes to the liver while interposition mesocaval and portacaval shunts resulted in preservation of 23–70% of hepatic portal blood flow. This continued oxygenation and nutrition of hepatocytes apparently preserves the remaining liver function and thus helps to prevent liver failure and encephalopathy. Encephalopathy was seen in only four (10%) of our 42 survivors, followed for more than a year, and was easily controlled by diet and lactulose therapy. This low incidence of encephalopathy associated with interposition grafting has previously been noted by Drapanas[1] et al.,[9,10] Lord et al.,[19,20] Stipa et al.[35,36] and Filtzer et al.[15]

Patients with bleeding esophageal varices are such poor operative risks that every effort should be made to avoid surgery. Despite the use of balloon tamponade, fresh whole blood and vasopressin, we found it necessary to operate on 13 patients to prevent exsanguination. Five (38%) died in the early postoperative period. This mortality is less than the 57% reported by Prandi et al.[27] when emergency portacaval shunting was carried out and the 45% reported by George et al.[14] and 55% reported by Pugh[29] when variceal ligation are so disappointing that a "jump" graft from the portal to systemic circulation should be used in emergency situations to treat variceal hemorrhage. There is no doubt that interposition grafting requires less dissection, fewer transfusions and less anesthesia than either direct mesocaval or portacaval anastomosis. Early in our study we used prosthetic material in emergencies but became disappointed with the results as two grafts clotted early. We now use the interposition autograft exclusively when operating for acute bleeding.

In our 42 elective operations there was one hospital death (2.4%). This low mortality is in agreement with Drapanas et al.,[9,10] and Fitzler et al.[15] using prosthetic material and Stipa et al.[36] using autografts for interposition. Which material should be used for the "H" graft? Lord et al.[19,20] using Teflon® for mesocaval interposition had one instance of occlusion in seven patients observed up to 20 months while Drapanas et al.[10] reported a 95% patency rate in 80 patients followed up to five-and-one-half years. Thrombosis occurred in two of our five patients with Dacron grafts. Technical factors can contribute to thrombosis. Drapanas[9] pointed out the necessary rotation required to relate the conformity of the vena cava and mesenteric vein. We found inter pancreaticoduodenal placement to be thrombogenic because of compression from both hemorrhage and pancreatitis.[31] Autogenous vein is pliable, flexible and causes less tissue reaction than prosthetic material which is more likely to kink and is known to produce mural thrombi. We now use autogenous jugular vein exclusively.

The use of autogenous internal jugular vein as an "H" grafting material seems ideal. It is always available, easy to obtain, is "surplus" and as previously shown experimentally by Dale and Scott[8] as well as Betancourt et al.[1] evokes the least tissue reaction and is, therefore, less likely to clot. In all our cases it has been long enough to bridge the defect and is of sufficient diameter (1 cm or greater) to shunt an adequate amount of blood to reduce portal pressure significantly but yet allow some continuing hepatic portal blood flow. There have been no known occlusions in the seven years since we have used autogenous vein. Eight such grafts were found patent at autopsy, 18 on angiography and 15 other patients remain asymptomatic. Although we have used the mesocaval rather than the portacaval shunt exclusively since 1975, as it is easier to perform, one must be prepared to perform either since rare anomalies of the mesenteric vein and its tributaries apparently exist,[18] even though we have not encountered them, and may produce technical problems and prolong the procedure in these debilitated patients. Theoretically, the mesocaval shunt is to be preferred over the protacaval shunt because it prevents augmentation of the hyperdynamic state seen in cirrhotic patients and is more likely to protect against post-shunt encephalopathy. However, with equal numbers (19 of each) of mesocaval and portacaval "H" shunts we noted no difference in the incidence of encephalopathy or long term survival.[39] Reynolds,[33] Bismuth et al.,[3] and Burchell et al.[4] have pointed out that the type of shunt, whether partially or totally diverting, had little to do with the eventual outcome in these alcoholic patients.

Hypertrophy of the caudate lobe in cirrhotic patients may cause marked caval hypertension (pressure greater than 240mm H_2O).[25,42] When standard portasystemic shunting is carried out resulting decompression is minimal. In two of our patients with interposition grafting the fall in portal pressure was negligible and in the postoperative period both had increasing ascites and icterus with associated renal failure that resulted in death. Interposition as well as standard portasystemic is contraindicated if the vena cava pressure exceeds 240mm H_2O. Other procedures such as interposition grafting between the splenic vein and left inferior pulmonary artery[12] or the splenic vein-right atrial shunt[21] may prove to be a more satisfactory solution to this complicated hemodynamic problem.

Lord et al.[20] and Drapanas et al.[10] and Filtzer et al.[15] report few complications follow interposition grafts. Most of our patients continue to drink heavily after their operations and we, therefore, see not only the complications usually noted after direct shunts but also those of alcoholism. Duodenal ulcers have developed in six patients leading to death from hemorrhage in one and perforation in another; bleeding from alcoholic gastritis was seen in two, fatal pancreatitis in one and deteriorating liver function, aspiration pneumonia, and eventually death in five additional late survivors. It is of particular interest that three patients developed primary carcinoma of the liver and died within two years of operation. Purtilo and Gottlieb[30] have reported that cirrhosis and hepatoma are increasing in the United States. They further noted that an average of eight years ensued from the onset of alcoholic cirrhosis and the appearance of hepatoma in 23 patients. MacDonald[22] has reported variceal hemorrhage associated with hepatoma in 16%. We recommend that the liver be carefully examined and biopsy be performed at the time of shunting to rule out this entity.

In conclusion, our experience with the principle of interposition "H" grafting coupled with that of others indicates that this is an acceptable means of simplifying the operation for portal decompression. The incidence of post shunt encephalopathy is low possibly due to continued perfusion of hepatocytes via the portal vein. Long term data are difficult to accumulate and evaluate because other aspects of these patients disease, especially alcoholism, lead to death from causes other than bleeding.

References

1. Betancourt, J. R., Hirsh, E. F. and Estes, J. T.: Portacaval Shunts: Experimental Use of Various Grafting Materials Constructing a "Y" Shape Shunt. Am. Surg., 35:516, 1969.
2. Bismuth, A., Franco, D. and Hepp, J.: Portal-systemic Shunt in Hepatic Cirrhosis: Does the Type of Shunt Decisively Influence the Clinical Result? Ann. Surg., 179:209, 1974.
3. Blakemore, A. H. and Lord J. W., Jr.: Technique for Using Vitalluim Tubes in Establishing Portacaval Shunts for Portal Hypertension. Ann. Surg., 122:476, 1945.
4. Burchell, A. R., Moreno, A. H., Panke, W. F. and Nealon, T. F.: Hemodynamic Variables and Prognosis Following Portacaval Shunts. Surg. Gynecol. Obstet., 138:359, 1974.
5. Child, C. G., III,: Eck's Fistula. Surg. Gynecol. Obstet., 96:375, 1953.
6. Child, C. G., III, (ed.): The liver and portal hypertension. Problems in Clinical Surgery, Vol. I. Philadelphia, W. B. Saunders Co., 1964, p. 50.
7. Clatworthy, H. W., Jr., Wall, T. and Watman, R. N.: New Type of Portal-to-systemic Venous Shunt for Portal Hypertension. Arch. Surg., 71:588, 1955.
8. Dale, W. A. and Scott, H. W., Jr.: Grafts of the Venous System. Surgery, 53:52, 1963.
9. Drapanas, T.: Interposition Mesocaval Shunt for Treatment of Portal Hypertension. Ann. Surg., 176:435, 1972.
10. Drapanas, T., LoCicero, J. III and Dowling, J. B.: Hemodynamics of the Interposition Mesocaval Shunt. Ann. Surg., 181: 523, 1975.
11. Filtzer, H. S., Rossi, R. and Wolfort, F. G.: Experience with Interposition Mesocaval Shunt for Management of Variceal Bleeding. Arch. Surg., 112:593, 1977.
12. Fonkalsrud, E. W., Linde, L. M. and Longmire, W. P., Jr.: Portal Hypertension from Idiopathic Superior Vena Caval Obstruction. JAMA, 196:129, 1966.
13. Foster, J. H., Jelly, P. C., Symbas, P. N. and Dively, W. L.: Vein Grafting in Portal Venous System. Arch. Surg., 91:716, 1965.
14. George, P., Brown, C., Ridgway, G., et al.: Emergency Oesophageal Transection in Uncontrolled Variceal Haemorrhage. Br. J. Surg., 60:635, 1973.

15. Giles, G. R., Brennan, T. G. and Losowsky, M. S.: Interposition Teflon Mesenteric Caval Shunt for Bleeding Oesophageal Varices. Br. J. Surg., 60:649, 1973.
16. Gliedman, M. L. and Margulies, M.: The Side-to-end Superior Mesenteric Vein-inferior Vena Cava Shunt for Portal Decompression. Surgery, 56:473, 1964.
17. Harmon, J. W., Zinner, M. J. and Reynolds, D. G.: Comparison of Portal Flow Distribution After Portacaval and Mesocaval Shunts. J. Surg. Res., 22:343, 1977.
18. Holyoke, E. A., Davis, W. C. and Harry, R. D.: Surgical Anatomy of the Mesocaval Shunt. Surgery, 78:526, 1975.
19. Lord, J. W., Jr., Rossi, G., Daliana, M. and Rosati, L. M.: Mesocaval Shunt Modified by the Use of a Teflon Prosthesis. Surg. Gynecol. Obstet., 130:525, 1970.
20. Lord, J. W., Jr., Rossi, G., Daliana, M. and Rosati, L. M.: Portasystemic Shunts in the Management of Massive Hemorrhage from Esophageal Varices Due to Cirrhosis of the Liver. Am. J. Surg., 121:241, 1971.
21. Luttwak, E. M., Charuzi, J., Licht, A., et al.: Emergency Spenic Vein-right Atrial Shunt for Massive Esophageal Hemorrhage with Cirrhosis of Liver and Inferior Vena Cava Occlusion: Report of an Operation and Follow-up. Ann. Surg., 177:411, 1973.
22. MacDonald, R. A.: Primary Carcinoma of the Liver; a Clinical Pathologic Study of One Hundred Eight Cases. Arch. Intern. Med., 99:266, 1957.
23. Malt, R. A.: Porta Systemic Venous Shunts (second of two parts) N. Engl. J. Med., 295:80, 8 Jul, 1976.
24. Marion, P.: Traitement Chirurgical de l'Hypertension Portale. Helv. Med. Acta., 21:375, 1954.
25. Mullane, J. F. and Gliedman, M. L.: Elevation of the Pressure in the Abdominal Inferior Vena Cava as a Cause of Hepatorenal Syndrome in Cirrhosis. Surgery, 59:1135, 1966.
26. Nabseth, D. C., O'Hara, E. T., Marks, L. J. and Mehrez, I. O.: The "H" Graft in Portacaval Shunts. Ann. Surg., 168:201, 1968.
27. Prandi, D., Rueff, B., Roche-Sicot, J., et al.: Life-threatening Hemorrhage of the Digestive Tract in Cirrhotic Patients. An Assessment of the Post Operative Mortality After Emergency Portacaval Shunt. Am. J. Surg., 131:204, 1976.
28. Preston, F. W. and Trippel, O. H.: The Technique of Emergency Portacaval Shunt. Surg. Clin. North Am. 46:37–53, Feb. 1966.
29. Pugh, R. N. H., Murray-Lyon, I. M., Dawson, J. L., et al.: Transection of the Oesophagus for Bleeding Oesophageal Varices. Br. J. Surg., 60:646, 1973.
30. Purtilo, D. T. and Gottlieb, L. S.: Cirrhosis and Hepatoma Occurring at Boston City Hospital (1917–1968). Cancer, 32:458, 1973.
31. Read, R. C., Thompson, B. W., Wise, W. S. and Murphy, M. L.: Mesocaval H Venous Homografts. Arch. Surg., 101:785, 1970.
32. Reynolds, J. T. and Southwick, H. W.: Portal Hypertension; Use of Venous Grafts When Side to Side Anastomosis is Impossible. Arch. Surg., 62:789, 1951.
33. Reynolds, T. B.: Editorial: Promises, Promises. Hemodynamics and Portal-systemic Shunt. N. Engl. J. Med., 290:1484, 1974.
34. Spencer, F. C.: Discussion: Interposition Mesocaval Shunt in the Treatment of Portal Hypertension. Ann. Surg., 176:447, 1972.
35. Stipa, S., Thau, A., Cavallaro, A. and Rossi, P.: A Technique for Mesentericocaval Shunt. Surg. Gynecol. Obstet, 137:285, 1973.
36. Stipa, A., Thau, A., Ziparo, V. et al.: Mesenterico-caval Shunt with Jugular Vein for Portal Hypertension. Bull Soc. Int. Chir., 34(3): 179, 1975.
37. Thompson, B. W. and Read, R. C.: Use of the Autogenous Jugular Vein for Interposition Grafting in Portal Hypertension. South Med. J., 66:818, 1973.
38. Thompson, B. W. and Read, R. C.: Interposition "H" Grafting for Portal Hypertension. Arch. Surg., 108:502, Apr. 1974.
39. Thompson, B. W., Read, R. C. and Casali, R. E.: Interposition Grafting for Portal Hypertension. Am. J. Surg., 130(6):733, 1975.
40. Valdoni, P.: L'ipertensione Portale; Orientamenti e Indicazioni Curative Nell" Ipertensine Portale. Riforma Med., 68:1414, 1954.
41. Voorhees, A. B., Jr. and Blakemore, A. H.: Clinical Experience with the Superior Mesenteric Vein-inferior Vena Cava Shunt in the Treatment of Portal Hypertension. Surgery, 51:35, Jan. 1962.
42. Welling, R. E. and McDermott, W. V., Jr.: Combined Caval and Portal Hypertension with Cirrhosis of the Liver. A Problem in Management. Ann. Surg., 177:164, 1973.
43. Whipple, A. O.: Problem of Portal Hypertension in Relation to Hepato-spenopathies. Ann. Surg., 122:449, 1945.
44. Yeoh, K. S. and Eiseman, B.: Portal Vein Thrombosis: Thromboectomy and Porta-caval Anastomosis with the Use of a Graft. Singapore Med. J., 3:64, 1962.

DR. JERE W. LORD, JR. (New York, New York): These two papers by Dr. Thompson and Dr. Cameron are most provocative, and bring up so many points that I'd like to just touch on three at this time.

They emphasized not operating on emergency cases. I agree that one should control the hemorrhage in every possible way, rather than go ahead and do an emergency shunt. Dr. Orloff's data, which is based on operating as an emergency on every patient, reveals a 48% hospital mortality. If we select patients, and treat some of them conservatively during the emergency phase and operate electively, or semielectively, as Dr. Cameron pointed out, the mortality rate is a great deal lower.

Secondly, the concept of evaluating hepatic reserve by Child's method is important. I think the A and B patients should be operated upon, and the C's should be treated conservatively, if possible; and in some of these it is possible to bring them into a B status, and lessen the risk. The last point I would like to make is with regard to the material used for the interposition shunt. Dr. Giuseppe Rossi, one of my colleagues, did the first interposition shunt in this country, I believe, if not in the world, in 1964, as an emergency and used woven Teflon. My interest in the interposition shunt first came in 1967. I had the privilege of being a visitor at the Union Memorial Hospital in Baltimore and an excellent senior resident was planning to do a portacaval shunt. Instead I persuaded him to do an end-to-side mesocaval shunt. After one hour of trying to get enough length of the inferior vein to make this union, I wished to heaven I'd allowed him to do the end-to-side portacaval. In any case, ultimately he did an excellent job, and the patient did well. I learned subsequently that he decided, after this experience to go into hand surgery. I'm referring to Dr. Shaw Wilgis who is one of the new members of this Association.

After getting home, I then started to use women Teflon and Drs. Rossi, Daliana and I have a series of 45 patients. In 19 of them, which were performed as emergencies, the mortality rate was approximately 50%. In the other 26, performed electively or as semiemergencies, there was one death. There have been five closures, two due to poor surgical technique. In one the graft was placed above the duodenum and below the pancreas and this probably kinked and thrombosed. The other technical failure was due to the inadvertent suture of the two sides of the prosthesis, which is not recommended. The other three closed spontaneously, after proven patency by angiography, some time between four weeks and two years.

Eighteen millimeters woven Teflon is the same size as the 18 mm Dacron that Dr. Cameron referred to and Dr. Drapanas used. We have used in femoro-popliteal arterial bypasses during the last few months the Gortex graft, which was originally developed for venous occlusions by Dr. Eiseman and others. Mr. Hoover of the Gortex Company told me last week that two surgeons: Andrew Callow in Boston—who has performed ten interposition shunts with the Gortex graft, 10 mm in diameter, and Dr. Charles Currier in Washington who has performed some 25 procedures using a 16 mm prosthesis. Only one of these grafts occluded postoperatively.

The point is that the woven Teflon and Dacron form thick intimas, therefore a large size is necessary and this means that one must dissect at least 25 mm of superior mesenteric vein. That can be difficult under some circumstances. The Gortex graft forms a very thin intima and therefore a 10–14 mm size would make the dissection of the vein easier.

I wonder if either of the speakers have used the Gortex graft, and if so, how did the grafts perform.

DR. JOHN H. C. RANSON: We have recently reviewed our experience with this type of shunt over the past six years, and compared it to the results of standard portacaval shunts during the same period. 38 patients had mesocaval interposition shunts, and 55 had portacaval shunts for variceal bleeding during this time.

Overall in-hospital mortality was somewhat lower for mesocaval shunts than for portacaval shunts. Since, however, the mortality is related, at least in part, to the patient population being treated, we have attempted to identify the subgroup of patients for whom the mesocaval shunt may be superior.

Fifty-one patients having one of these two shunts were operated upon urgently because of failure of non-operative control of bleeding, and in this group mesocaval shunts reduced mortality from 58 to 33%. As Dr. Cameron has emphasized, hepatic reserve has been, perhaps, the most important determinant of survival, and in 27 Child's Group A or B patients there was one death, or a 4% mortality. In Child's C patients, however, mesocaval shunts reduced mortality from 51 to 36%.

Our experience, therefore, supports that reported tonight by Dr. Thompson and Dr. Cameron. In-hospital mortality remains very high for patients operated upon as emergencies, or with poor hepatic reserve, but in these two groups mesocaval interposition grafts appear to be superior to portacaval shunts, at least in terms of operative mortality. We found that the mean operative times for the two shunts were about equal, and the average operative blood replacement was only slightly greater for the portacaval shunts. I would like to ask, therefore, whether the authors feel that there may be some other explanation for the apparent superiority of mesocaval shunts.

DR. G. RAINEY WILLIAMS (Oklahoma City, Oklahoma): I will address my comments particularly to Dr. Cameron's beautiful presentation. On the basis of a smaller number of patients, fortunately, this problem is not as common in Oklahoma as it apparently is elsewhere—we substantially agree with what he has said, and particularly with limiting portacaval shunting to emergency patients.

Secondly, our own data support the fact that the severity of liver disease is the principal determinant in outcome.

And finally, somewhat at variance with what Dr. Ranson has said, the mesocaval shunt is technically a good deal easier in our hands, and has given a better mortality rate.

And finally, I'd like to ask Dr. Cameron whether or not he's used balloon tamponade, which we continue to think is helpful in getting the patient to the operating room.

DR. ROBERT ZEPPA (Miami, Florida): I rise, obviously, to support a distinctly different point of view.

I think, first of all, that Dr. Thompson's allusion to the dog studies with the microspheres presents a comparison of microsphere utilization where there is no increased resistance in the liver. The prediction for humans remains yet to be solved.

But more important, I think, is our difference of opinion with respect to the emergency patient. We would not consider operating on most of our patients who come in bleeding as emergencies, as I think Dr. Cameron has indicated. We would utilize both Pitressin, the Sengstaken-Blakemore tube, and clotting of the coronary vein, in an attempt to buy time.

As of last week, there were 100 elective patients done with the distal splenorenal shunt in our institution by my colleagues and I, and there were 23 who were not included in the series I showed you here, who were done on an emergent basis; that is, out of the schedule, continuing to bleed, either going to the operating room with Pitressin and/or both the Sengstaken-Blakemore tube.

The mortality here is three patients, and that's considerably higher than the 1% mortality we have for the elective procedure.

So I think that it's much more important to try to stop patients' bleeding, to get them to the operating room under elective circumstances.

One more comment about the incidence of encephalopathy. There must be a vast difference between encephalopathy in the United States and encephalopathy in England, because their evaluation of the mesocaval shunt shows exactly the same encephalopathy that they saw with patients who had portacaval shunt.

And I would also like to remind you of Dr. Voorhees' article which was published in the *American Journal of Surgery* some years ago, in which he reviewed the 26 year experience from Columbia, and he concluded that 60% of his patients, whether they had splenorenal shunts of the classical variety, which is a small total shunt, or the portacaval shunt, led to the development of encephalopathy in that percentage that I've indicated.

And this is a surprising figure, because it fits perfectly with the information that's come from the use of the portacaval shunt in patients with schistosomiasis. Sixty per cent of these patients within two years will show the angiographic disturbances which can be identified as cirrhosis, and 60% of the patients who didn't have hepatocellular disease to start with end up with encephalopathy and hepatocellular disease.

DR. W. DEAN WARREN (Atlanta, Georgia): I simply was going to rise to give you some information from Brazil which is of tremendous importance to those studying this problem. However, before doing so, I would like to comment to Dr. Thompson: The use of dogs with a normal intrahepatic sinusoidal pressure in no way duplicates the cirrhotic.

The other bit of information is: In our randomized series, in which we have brought back and restudied angiographically at an average length of time of three years, the only three patients out of 28 who perfused the liver with a mesocaval shunt are those three which have thrombosed the shunt, which is just exactly what was predictable.

Now for the information that I rose to give.

There is an outstanding surgeon in Sao Paulo, Brazil, Dr. Silvano Raia, who is very much interested in portal hypertension. He and many other surgeons in Brazil have more personal experience in the management of variaces than anyone in this audience, including Dr. Lord, who was there at the beginning, myself, Dr. Zeppa, Dr. Zuidema, and anybody you can think of.

They have now established one fact with certainty: The total deviation of portal flow, whether it be portacaval shunt and/or mesocaval shunt, is a catastrophe in the patient with schistosomias. And those are patients with excellent hepatic function but portal hypertension due to portal vein pathology. After those total shunts, the incidence of encephalopathy is not 10%, or 17%; it is 70%.

For the tremendous hepato-splenic schistosomiasis population in that country, estimated at 200,000, portacaval type shunts have been almost abandoned. They are now doing a prospective randomized study of the selective distal splenorenal shunt, the conventional splenorenal shunt, which has a lower incidence of encephalopathy, probably due to occlusion of the shunt, and a Womack-type of nonshunt procedure.

DR. GILBERT S. CAMPBELL (Little Rock, Arkansas): Earlier speakers have talked about surgical milestones in portal hypertension—I've heard more surgical millstones than I have milestones.

Have you ever wondered how Dean Warren came up with that selective shunt? You know, I can remember how he used to argue with Dr. Linton about the splenorenal shunt. Finally, Dr. Warren operated on a patient once that didn't have a patent portal vein, so he performed his first splenorenal shunt. (Slide) Look at him—he is what you call a textbook surgeon with a step-by-step textbook of surgery.

I would like to stress something that Dr. Warren has forgotten. Twenty millimeters is double ten millimeters. Many of these autogenous jugular vein grafts are 10 mm or so in diameter so they are much smaller than large prosthetic H-grafts. The smaller grafts don't carry so much flow, and patients don't get so fuzzy in their head after this lesser procedure.

Finally, we want to agree with Dr. Warren. We too believe in selective shunts for portal decompression. However, we would select the patient's very own jugular vein to serve as an H-graft, because this safe jugular vein H-graft, as the British would say, "serves as an expedient conduit to transfer blood from the heavily congested portal venous system to the high-flow, low-pressure caval system."

Dr. Hiram C. Polk, Jr. (Louisville, Kentucky): Our reason in rising to comment on this is to describe a very useful clinical experience with the interposition shunt, essentially as described by Dr. Drapanas, and on the part of Dr. Ahmad and Dr. Harbrecht. From our V.A. service largely, they have recently described an experience with about 22 patients. We have been very comfortable with this operation as an expeditious, effective, slightly traumatic operation in the ill patient, the Child B or C classification that is least likely to do well.

Our patients have done well, and we have been very pleased with operation clinically.

However, to test the thesis involved that continued perfusion of the hepatic limb of the shunt exists, we have made a number of tests, and I can simply summarize those by what's been said tonight. We have not been able to show hepatopedal flow in a single individual under any circumstance.

I think it is an expedient shunt that's useful to people who do not do the large numbers of shunts, such as those described in Brazil. We're comfortable with it.

I think the metabolic advantages of it are less real than theoretic. I think the reference to the work by Harmon and his associates just underlines the fact that in the normal liver, and the normal portal circulation, hepatopedal blood flow does continue, but in the cirrhotic situation it never occurs, and I doubt will ever be documented in man.

Dr. Bernard W. Thompson (Closing discussion): First of all, I would like to thank Dr. Lord, as he has had a very vast experience with the interposition graft. I would like to agree with him, that we use every means possible to stop the acute bleeding, tamponade, vasopressin, and so forth. We do prefer to delay our operation some two to six weeks, if at all possible.

We do our operation a little differently than any of these that have been shown, and it's in our manuscript. We actually place the end of our H-graft in the inferior vena cava much lower, almost at the confluence of the iliac veins to get around the sweep around the duodenum, which several have reported in the past has caused venous obstructions at the duodenum.

I also would like to tell Dr. Lord that some time ago I did obtain from the Gortex people a 16 mm PTFE graft, but since then I have not had a chance to use it, but if we do, we will probably report how we do with it.

I would then like to mention, to answer Dr. Ranson's question, that we, like Dr. Williams from Oklahoma, have found that in our hands the H-graft takes much less time, we lose much less blood, and in several of our patients have not given any blood at all—in the elective cases, of course.

As far as Drs. Zeppa and Warren are concerned, I would like to just mention that we brought up this study that's been carried out by Dr. Harmon to bring up the possibility that maybe there is flow to the liver in man when an H-graft is performed. We agree that this study using experimental animals is not comparable to man, because we do have a normal sinusoidal pressure, which is different from the patient with portal hypertension.

And I would like to also mention to Dr. Warren, and agree with what he says about the patients from Brazil. The Mayo Clinic in the past has inferred in some of their studies that the patients with the more normal liver function after a portacaval shunt have the most encephalopathy. There is almost an inverse incidence of good results after shunting. In those having poor liver functions, there is a low incidence of encephalopathy.

Ten Years Experience with Intravenous Hyperalimentation and Inflammatory Bowel Disease

JAMES L. MULLEN, M.D., W. CLARK HARGROVE, M.D., STANLEY J. DUDRICK, M.D.,
WILLIAM T. FITTS, JR., M.D., ERNEST F. ROSATO, M.D.

From the Department of Surgery,
University of Pennsylvania School of Medicine and the
Philadelphia Veterans Administration Hospital,
Philadelphia, Pennsylvania

A retrospective analysis was conducted on 74 patients with inflammatory bowel disease who were treated with intravenous hyperalimentation at the Hospital of the University of Pennsylvania between the years 1967–1976. Intravenous hyperalimentation can ameliorate the inevitable protein–calorie malnutrition present in patients with inflammatory bowel disease. Combined with complete bowel rest, intravenous hyperalimentation can effectively function as the primary treatment or as an adjunct to the surgical management of the complications of inflammatory bowel disease. Intravenous hyperalimentation can be safely administered to these severely ill patients, almost certainly improving survival rates in the patients treated.

MALNUTRITION CONSISTENTLY OCCURS in patients with inflammatory bowel disease (IBD). The catabolic effects of a chronic inflammatory process are combined with dysfunction of the gastrointestinal tract which impairs normal nutrient intake and absorption. These effects are readily apparent upon examination of the nutritional status of hospitalized patients with inflammatory bowel disease, particularly when complications of perforation, fistula or infection impose increased energy and caloric demands on the individual.[3,9,12] The malnourishing effects of inflammatory bowel disease[9,12] are multiple: 1) a substantial decrease in oral protein-calorie intake. This deficient intake is due to the anorexia associated with a chronic inflammatory disease and to avoidance behavior conditioned by the occurrence of gastrointestinal symptoms associated with eating; 2) a decrease in absorptive capacity secondary to extensive inflammatory disease of the intestine and to previous bowel resections. The ultimate effect of the malabsorption component will be determined by the capacity of the individual to increase his caloric and protein intake to compensate for these absorptive losses; 3) a substantial loss of visceral protein through diseased segments of bowel, placing an increased demand on protein synthesis mechanisms and substrate availability; 4) increased energy-caloric demands generated by the hypermetabolic effects of the inflammatory process and by complications such as infection and peritonitis.

In addition to the malnourishing effects of the disease process, the treatment for the primary disease significantly increases the nutritional burden of the already compromised host.[11] A reduction in food intake and often complete bowel rest are employed during an acute exacerbation of symptoms in the patient with inflammatory bowel disease. This severely limits nutrient intake. The usual attempts at protein-calorie supplementation using specialized enteral feeding techniques are often unsuccessful in meeting nutritional needs. Corticosteroids are often administered to these patients, particularly those with severe disease. The side effects of these anti-inflammatory agents include general catabolic effects, poor wound healing and reduced host resistance to sepsis.[10] Surgical procedures are often required in the treatment of inflammatory bowel disease, producing further malnourishing effects such as a decrease in absorptive surface, mandatory gastrointestinal dysfunction in the perioperative period and the hypermetabolic effects of major surgical trauma.

The employment of adequate nutritional support in the patient with inflammatory bowel disease is easily justified in view of these multiple factors which lead to malnutrition.[7,9,12] The adverse effects of nutritional depletion on the patient's course are substantial. Increased disease/treatment morbidity and mortality[10] and decreased therapy response rate occur in *malnour-*

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests: James L. Mullen, M.D., 4th Silverstein Pavilion, Nutrition Support Service, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

Supported in part by an Educational Grant from McGraw Laboratories, Santa Ana, California.

0003-4932-78-0500-0523-0085 © J. B. Lippincott Company

TABLE 1. *Disease Site, Age, Duration Hospital Stay*

Site	# Patients	Age (Years)*	Hospital Stay (Days)*
Ulcerative Colitis (UC)	24	44 ± 3.4	51.2 ± 6.0
Regional Enteritis (RE)	17	36 ± 3.8	32.0 ± 2.5
Granulomatous Colitis (GC)	8	31 ± 5.1	42.3 ± 7.6
RE and GC	25	32 ± 2.5	41.7 ± 4.4
Entire Population	74	37 ± 3.4	42.6 ± 4.7

* Mean ± SEM.

ished patients with inflammatory bowel disease. The repletion of nutritional deficits and the maintenance of adequate nutrition combined with complete bowel rest during an acute inflammatory episode may provide the additional benefits of avoiding surgery and reducing the length of hospitalization.[7]

Patients with inflammatory bowel disease and substantial decreases in voluntary oral food intake can be force-fed through two routes—enteral and parenteral. Although isolated successes[13,15] have been reported via the enteral route, most nutritional support has been provided via total parenteral nutrition or intravenous hyperalimentation (IVH), particularly where complete bowel rest is a necessary component of the therapeutic regimen.[7,9,12] Since its inception at this institution,[4] intravenous hyperalimentation has been utilized extensively in patients with inflammatory bowel disease. Some of the initial patients treated with IVH had extensive granulomatous disease of the intestine and early results were gratifying. This report encompasses our experiences in providing parenteral nutritional support to patients with inflammatory bowel disease during the past ten years, 1967 through 1976. The report covers the spectrum from the early years when IVH was a last resort to the more recent years when nutritional support has been instituted at an earlier stage.

Clinical Material

From 1967 through 1976, adequate records were available for retrospective analysis on 293 patients who had 617 admissions to the Hospital of the University of Pennsylvania with a primary diagnosis of inflammatory bowel disease (2.1 admissions per patient). Seventy-four patients (25%) were referred to the Surgical Service for nutritional evaluation and support with intravenous hyperalimentation. These 74 patients underwent 117 courses of intravenous hyperalimentation. Twenty-four patients (32%) had ulcerative colitis and the remaining 50 patients (68%) had granulomatous disease of the small bowel, colon or combined disease of both. In certain instances, it is difficult, if not impossible, to differentiate between ulcerative colitis and granulomatous disease of the colon but the assigned diagnoses were based upon combined clinical, radiologic and pathologic criteria.[11,16]

The mean age of the 74 patients was 37 years. The duration of hospital stay was 43 days. Patients with granulomatous disease were somewhat younger and had a shorter hospital stay (Table 1). A retrospective analysis was conducted on the records of these 74 patients to determine admission nutritional status, presenting disease severity, indications for nutritional support, effects and morbidity of IVH, specific effects of IVH on enterocutaneous fistulas, operative morbidity and mortality, indications for continued nonoperative treatment, and follow-up of postdischarge course.

Results

Assessment of the nutritional status of the 74 patients referred to the Surgical Service for consideration of parenteral nutritional support revealed a moderately-to-severely malnourished population (Table 2). This malnutrition could be classified as marasmic-kwashiorkor type with significant depletion of body-cell mass reflected in the substantial weight loss (19 ± 3 lbs), and substantial depressions in the visceral protein component, as shown by serum albumin levels of 2.9 ± 0.13 g% and serum transferrin levels of 158 ± 13.2 mg% (Table 2). Sixty-three (82%) of the patients suffered a loss of body weight greater than 10% of their usual weight, an amount generally agreed to indicate significant malnutrition. There were no substantial differences in the various nutritional parameters between types of inflammatory bowel disease.

These patients represented a selected group from

TABLE 2. *Nutritional Status*

	# Patients	Weight Loss (lbs)	>10% Weight Loss	Albumin (g%)*	Transferrin (mg%)*
UC	24	20 ± 3.1	21 (88%)	2.7 ± 0.14	143 ± 12.6
RE	17	21 ± 4.2	14 (78%)	3.0 ± 0.13	150 ± 14.0
GC	8	16 ± 2.6	7 (88%)	2.8 ± 0.21	163 ± 16.2
RE & GC	25	17 ± 2.1	21 (78%)	3.0 ± 0.09	177 ± 12.4
Total	74	19 ± 3.0	63 (82%)	2.9 ± 0.13	158 ± 13.2

* Mean ± SEM.

TABLE 3. *History of Previous Surgery*

Site	# Patients	Interval to Present Adm. (Yrs)	Indication				
			Infl	Hem	Perf	Fist	Obst
UC	2 (8%)	10.0	0%	0	100%	0%	0
RE	6 (33%)	4.7	17%	0	17%	33%	17%
GC	2 (25%)	2.0	50%	0	50%	0%	0%
RE & GC	15 (56%)	7.1	40%	7%	33%	13%	13%
Total	25 (32%)	6.2	32%	4%	40%	16%	12%

the total population of IBD patients seen at our hospital in that the severity of disease was greater. Twenty-five of the 74 patients (32%) had undergone a previous intra-abdominal procedure. The mean duration from the previous operation to the present admission was 6.2 years. Almost all patients (92%) who had a previous operation were individuals with granulomatous disease. Two patients with ulcerative colitis had previous emergency operations because of a perforated toxic colon. Those patients with granulomatous disease (23 of 25) were operated on previously for the following indications: intractable inflammation (32%), perforation (40%), fistula (15%), obstruction (12%) and hemorrhage (4%) (Table 3). The patients' inpatient therapy regimen before receiving IVH was often of the multiple drug variety, usually including steroids, salicylazosulfapyridine (Azulfidine), and opiates. Only 14% of these patients were not receiving any of these medications (Table 4). Twenty-five (34%) of the 74 patients had a total of 43 enterocutaneous fistulas, 20 of the 50 patients with granulomatous disease (40%) and five of the 24 patients with ulcerative colitis (21%). Four of the six fistulas in the ulcerative colitis group followed operations for drainage of abscesses following perforation.

The indications for parenteral nutritional support were varying and often multiple. Nutritional preparation for operation was the reason in 33% of the patients, and failure of medical treatment was the indication in 61%. The poor nutritional status of the patient was cited as an indication for nutritional support in only 48% of these patients (Table 5).

Intravenous hyperalimentation improved the nutritional status or prevented further deterioration in almost all patients. Seventy-seven per cent of these patients gained weight on IVH despite the presence of an acute inflammatory process or other complications. Only eight patients *lost* weight and this was of little magnitude. The average duration of intravenous hyperalimentation was three and one-half weeks (26 ± 3.7 days) with no substantial differences between the types of disease. The average amount of weight gain was 10 lbs during this three and one-half week period (Table 6).

TABLE 4. *Medical Regimens—Admission (Pre-IVH)*

Site	None	Steroids	Azulf	Opiates
UC	8%	50%	58%	50%
RE	17%	39%	44%	39%
GC	12%	50%	37%	50%
RE & GC	19%	48%	48%	70%
Totals	14%	51%	51%	57%

TABLE 5. *Indications for IVH*

Site	Pre-op	Failed Med Rx	Nutritional
UC	29%	67%	58%
RE	39%	44%	50%
GC	25%	88%	25%
RE & GC	37%	48%	48%
Totals	32%	61%	48%

The beneficial effects of IVH were accomplished with minimal morbidity, no different from that experienced in the non-IBD patient population treated with IVH in our hospital. Complications occurred in eight patients (10%): three episodes of pneumothorax (4%); three instances of catheter sepsis (4%); and two episodes of metabolic complications (2%). No mortality was attributed to IVH (Table 7).

Forty-six (62%) of the 74 patients had surgery during their course of intravenous hyperalimentation, 15 of 24 in the ulcerative colitis group (62%) and 31 of 50 in the granulomatous disease group (62%). Almost 40% of patients who had previously failed on a medical regimen had an IVH-induced remission compatible with hospital discharge without operation; this success rate is similar to the other series.[7] An intractable inflammatory process was the most common indication for operation (Table 8). Ten patients had operative complications (22%) which were often multiple —fistula, sepsis and wound infections leading to death in four (9%) individuals (Table 9). Seventeen of the 43 fistulas (43%) were closed with IVH alone, thus avoiding any surgical procedure. Only three of these recurred, leaving an overall permanent fistula closure rate with intravenous hyperalimentation alone of 33% (Table 10). All patients (26) with fistulas that did not

TABLE 6. *Weight Change—IVH*

	None	Gain	Loss	Duration (Days)*
UC	8%	84%	8%	29 ± 4.4
RE	11%	83%	6%	22 ± 2.5
GC	12%	88%	0%	19 ± 4.6
RE & GC	26%	63%	11%	29 ± 3.8
Totals	15%	77%	8%	26 ± 3.7

* Mean ± SEM.

TABLE 7. *IVH Complications*

	None	Metabolic	Pneumothorax	Catheter Sepsis
UC	87%	4%	4%	4%
RE	83%	0%	11%	5%
GC	100%	0%	0%	0%
RE & GC	93%	4%	0%	4%
Totals	90%	2%	4%	4%

TABLE 9. *Operative Complications*

	# Ops	Deaths	Sepsis	Fistula	Wd Infect
RE	9	0%	11%	11%	11%
UC	15	20%	40%	20%	20%
GC	3	0%	0%	0%	33%
RE & GC	19	5%	15%	5%	0%
Totals	46	9%	22%	11%	11%

close with IVH alone underwent surgical closure. All of these were successfully closed at the time of operation. However, three subsequently recurred in the postoperative period in the hospital or postdischarge (Table 11). Overall, of the 43 fistulas in 25 patients, all were closed initially with either IVH alone or as an adjunct to operation, although six recurred (three after IVH alone; three after IVH-surgery). The overall closure rate was 86% (37 of 43) (Table 12).

When surgical complications were analyzed with regard to preoperative medical regimens, there were no substantial differences in the complication rates. However, when the data was analyzed according to whether the disease process was ulcerative colitis or granulomatous disease (Table 13), substantial differences were apparent. In the 15 patients with ulcerative colitis who were operated on, there was a substantial increase in the complication rate of those *not* on preoperative steroid medication. Conversely, in the 31 patients undergoing operation for granulomatous disease, there appeared to be little difference in complications associated with the preoperative use of corticosteroids.

Almost all surgical procedures (87%) were resections; no bypass procedures were employed. Various other (13%) procedures were employed usually in emergency situations (Table 14).

When discharge (post-IVH) medical regimens (Table 15) were compared with initial regimens (Table 4) substantial decreases in medication are apparent.

During a six to 120 month follow-up period, 25 patients were readmitted to the hospital for recurrent disease: 20 with granulomatous disease and five with ulcerative colitis. Twelve had only one subsequent admission and 13 two or more admissions. During the readmission, 16 patients underwent 43 additional courses of IVH and 18 patients had 24 operations.

TABLE 8. *Surgery and IVH*

		Surgical Indications				
Site	No Surgery	Inflam	Hemm	Perf	Obstr	Fist
RE	50%	16%	6%	0%	6%	22%
UC	38%	42%	16%	4%	0%	0%
GC	63%	37%	0%	0%	0%	0%
RE & GC	34%	11%	7%	11%	11%	26%
Totals	38%	28%	9%	5%	5%	15%

Discussion

The malnourishing effects of inflammatory bowel disease are readily apparent from this series of patients, demonstrating significant losses of body cell mass from prolonged conversion of fat and skeletal muscle fuel reserves to satisfy the energy demands in these individuals with inadequate protein and calorie intake. Particularly noteworthy is the almost uniform depression of visceral protein with its impact on immunologic competence and ultimate sepsis and mortality. This particularly lethal combination of marasmic kwahiorkor-like malnutrition is usually associated with a substantial incidence of sepsis and ultimate mortality if untreated.[3,10]

The severity of inflammatory bowel disease in this series is not surprising since hyperalimentation was first utilized in these patients at this institution. As with most new treatments, initial patient referrals were often critically ill patients who were treatment failures and were given intravenous hyperalimentation as a last resort. As the efficacy of intravenous hyperalimentation in inflammatory bowel disease has been documented, nutritional support has been offered to these patients at an earlier stage, ameliorating the consequences of severe protein-calorie malnutrition. Although this has occurred to some extent, it is by no means the standard therapy applied in all patients with inflammatory bowel disease who have protein-calorie malnutrition. The rationale for the use of intravenous hyperalimentation in the patient with inflammatory bowel disease is three-fold: 1) to replete the nutritional deficits commonly seen; 2) to allow complete bowel rest with adequate protein-calorie intake;

TABLE 10. *Fistula Rx—IVH Alone*

	# Patients	# Fistula	# Closed (%)	# Recurred (%)
RE	10	15	5 (33)	1 (20)
UC	5	6	5 (83)	1 (20)
GC	2	2	2 (100)	0 (0)
RE & GC	8	20	5 (25)	1 (20)
Totals	25	43	17 (40)	3 (18)

TABLE 11. *Fistula Rx—IVH and Surgery*

	# Fistula	# Closed	# Recurred (%)
RE	10	10	1 (10)
UC	1	1	1 (100)
GC	0	0	0 (0)
RE & GC	15	15	1 (7)
Totals	26	26	3 (12%)

TABLE 12. *Fistula Rx—Summary*

	# Patients	# Fistula	# Initially Closed	# Recurred	# Perm Closed (%)
RE	10	15	5	2 (13)	13 (87)
UC	5	6	6	2 (33)	4 (67)
GC	2	2	2	0 (0)	2 (100)
RE & GC	8	20	20	2 (10)	18 (90)
Totals	25	43	43	6 (14)	37 (86)

TABLE 14. *Surgical Procedures*

	Bypass	Resection	Other
RE	0%	80%	20%
UC	0%	93%	7%
GC	0%	100%	0%
RE & GC	0%	84%	16%
Totals	0%	87%	13%

and 3) to provide adequate parenteral nutritional support as an adjunct to surgical intervention.[7,12]

IVH should be more useful in patients with granulomatous disease than in those with ulcerative colitis because of the high incidence of recurrence, and the lack of an operation that will effect a cure, as can be accomplished in ulcerative colitis. With granulomatous disease, every reasonable effort is made to accomplish successful nonoperative treatment, and surgery is reserved for complications of the disease. In granulomatous disease, IVH combined with total bowel rest has served as an effective primary modality of treatment. With ulcerative colitis, intravenous hyperalimentation usually functions as an adjuvant nutritional support for a curative surgical resection.

Intravenous hyperalimentation has revolutionalized the treatment of gastrointestinal fistulas, including those secondary to inflammatory bowel disease.[9] Until adequate parenteral nutritional became a reality, early operative intervention was advocated to avoid the inevitable severe protein-calorie malnutrition.[1,2,9] The presence of a fistula is no longer an absolute indication for surgery. IVH alone resulted in a 33% long-term fistula closure rate.

It must be emphasized that intravenous hyperalimentation should not alter the basic surgical principles of fistula management: 1) relief of distal obstruction; 2) removal of foreign bodies; 3) removal of the epithelialized tract; and 4) drainage of adjacent intra-abdominal abscesses. Using optimal timing of the surgical intervention[1,2,5] combined with total parenteral nutritional support and complete bowel rest, this series of patients demonstrates that a high percentage (86%) of these fistulas can be closed permanently. Although some have advocated the use of enteral elemental diets for distal intestinal fistulas[13,15] this has not proved uniformly successful in our hands.

TABLE 13. *IVH and Surgery—Surgical Complications and Steroids*

	Death	Sepsis	Fistula
Ulcerative Colitis			
Steroids	0%	0%	0%
No Steroids	17%	33%	8%
Granulomatous Disease			
Steroids	5%	11%	5%
No Steroids	0%	6%	0%

Despite the severe nutritional deficits and increased metabolic demands in these patients,[7,12] intravenous hyperalimentation has effectively improved their nutritional status, with over three-fourths of all patients showing weight gain. Serial serum albumin and serum transferrin levels were often unavailable for analysis or invalidated by intervening intravenous albumin infusions.

Although the indications for surgery are somewhat different than in other series,[6] this may merely reflect the selected nature of our group or differences in criteria for assignment for data analysis.

These critically ill patients have a substantial operative mortality and morbidity despite adequate nutritional support. The operative complication rate of 22% in part reflects the severity of illness in the patients treated with intravenous hyperalimentation at its early beginnings. The complications of IVH itself were surprisingly low despite the significant disease severity.[14] We attribute this low complication rate to a true team approach to these patients, with meticulous attention to a standard protocol for monitoring and management of patients receiving total parenteral nutrition.

When complication rates were analyzed for a rela-

TABLE 15. *Medical Regimens—Discharge (Post-IVH)*

Site	None	Steroids	Azulf	Opiates
UC	54%	33%	29%	8%
RE	39%	28%	11%	28%
GC	50%	37%	12%	0%
RE & GC	22%	52%	22%	52%
Totals	39%	35%	20%	26%

tionship between the use of preoperative steroids and operative mortality and morbidity, no differences were found between the steroid treated group and those not treated with steroids, as in Jalan's series.[8] However, when ulcerative colitis patients were analyzed separately from those with granulomatous disease, the preoperative use of steroids in the patient with ulcerative colitis substantially decreased the operative mortality and morbidity. Although this is an uncontrolled study with varying disease severity, the evidence is suggestive that steroids have no significant deleterious effects in patients with ulcerative colitis and may even have a beneficial effect in the preoperative control of the patient with an acutely inflammed colon.[8]

References

1. Aguire, A., Fischer, J. E. and Welch, C. E.: The Role of Surgery and Hyperalimentation in Therapy of Gastrointestinal —Cutaneous Fistulae. Ann. Surg., 180:393, 1974.
2. Aguire, A. and Fischer, J. A.: Intestinal Fistulas in Total Parenteral Nutrition. Fischer, J. E. (ed.) Boston, Little, Brown, 1976.
3. Clark, R. G. and Lauder, N. M.: Undernutrition and Surgery In Regional Ileitis. Br. J. Surg., 56:736, 1969.
4. Dudrick, S. J., Wilmore, D. W., Vars, H. M. and Rhoads, J. E.: Long-term Total Parenteral Nutrition with Growth, Development and Positive Nitrogen Balance. Surgery, 64:134, 1968.
5. Edmunds, L. H., Jr., Williams, G. M. and Welch, C. E.: External Fistulas Arising From the Gastrointestinal Tract. Ann. Surg., 152:445, 1960.
6. Farmer, R. G., Hank, W. A. and Turnbull, R. P.: Indications for Surgery in Crohn's Disease (Analysis of 500 cases). Gastroenterology, 71:245, 1976.
7. Fischer, J. E., Foster, G. S., Abel, R. M., et al.: Hyperalimentation as Primary Therapy for Inflammatory Bowel Disease. Am. J. Surg., 125:165, 1973.
8. Jalan, K. N., Prescott, R. J., Smith, A. N., et al.: Influence of Corticosteroids on the Results of Surgical Treatment of Ulcerative Colitis. N. Engl. J. Med., 282: 588, 1970.
9. MacFadyen, B. V., Dudrick, S. J. and Ruberg, R.: Management of Gastrointestinal Fistulas with Parenteral Hyperalimentation. Surgery, 74:100, 1973.
10. Meakins, J. L., Pietsch, J. B., Bubenick, O., et al.: Delayed Hypersensitivity: Indicator of Acquired Failure of Host Defenses in Sepsis and Trauma. Ann. Surg, 186:241, 1977.
11. Nugent, W. F.: Medical Management of Inflammatory Disease of the Colon. Symposium on Gastrointestinal Surgery.
12. Reilly, J.: Inflammatory Bowel Disease in Total Parenteral Nutrition. Fischer, J. E., (ed.) Boston, Little, Brown, 1976.
13. Rocchio, M. A., Cha, C. J. M., Haas, K. F. and Randall, H. T.: Use of Chemically Defined Diets in the Management of Patients with Acute Inflammatory Bowel Disease. Am. J. Surg., 127:469, 1974.
14. Ryan, J. A., Abel, R. M., Abbott, W. A., et al.: Catheter Complications in Total Parenteral Nutrition. N. Engl. J. Med., 290:757, 1974.
15. Votik, A. J., Echave, V., Feller, J. H., et al.: Experience with Elemental Diet in the Treatment of Inflammatory Bowel Disease: Is This Primary Therapy? Arch. Surg., 107:329, 1973.
16. Zetzel, L.: Granulomatous (Ileo) Colitis. N. Engl. J. Med., 282:600, 1970.

DISCUSSION

DR. FRANCIS C. NANCE (New Orleans, Louisiana): I think this is a very important study. It represents the tenth anniversary of the introduction of intravenous hyperalimentation at the University of Pennsylvania; and by definition they have the longest followup of patients managed by this technique.

We have had similar observations in treating patients with inflammatory bowel disease, particularly in patients with regional enteritis and granulomatous colitis. We have been gratified to see resolution of fistulas and what we think is reduction in the severity of disease.

I'd like to ask Dr. Fitts some specific questions. Have you seen any physical disappearance of the typical granulomatous lesions while the patient is on hyperalimentation? In other words, can this in any way be considered definitive therapy for regional enteritis or granulomatous colitis?

Our own clinical observations are that the patients with regional enteritis and granulomatous lesions respond better than patients with ulcerative colitis. Have you seen patients with florid ulcerative colitis who have not responded at all to hyperalimentation, except in a general increase in their nutritional support?

And are there times when persisting with hyperalimentation could be dangerous to the clinical course of the patient? In other words, when do you stop hyperalimenting and intervene surgically?

I think it's also a legitimate question and an important question to ask something about the cost of maintaining a patient for the times that you mentioned here of 20–25 days on hyperalimentation. Is that a significant factor in hospitalization?

Finally, I feel that no one who was at the University of Pennsylvania in that era can ignore the fact that there is at least one important name omitted from the list of authors, and that's my old chief, Dr. Rhoads, whose contributions to this field are obvious, but which, I think, ought to be acknowledged again.

DR. FRANCIS E. ROSATO (Norfolk, Virginia): I'd like to thank Dr. Fitts and the other pioneers at the University of Pennsylvania not only for the development of IVH, but for updating their informative and timely experience again.

There are a lot of points in this paper that are worthy of discussion: I'm going to emphasize a few, and attach some questions to them.

First of all, there has been a reported anergy in a fair percentage of patients with chronic inflammatory bowel disease, specifically in their nonreactivity to DNCB, and also in their failure to respond to the mitogen PHA. Along a similar track, there is a body of literature that supports the notion that there is a return to immune competence with intravenous hyperalimentation. I'm wondering if some of the improvement that one sees in patients with chronic inflammatory bowel disease treated by hyperalimentation might not be due partially, at least, to a restoration to immune competence.

Do you have any studies, Dr. Fitts, that would relate to measured immune parameters during the course of treatment?

A second point worth emphasizing, and one interprets this from the slide, is that about half the patients that were referred for hyperalimentation were referred primarily for surgery, and only about half primarily for nutritional reasons. Therefore, I assume that in the process of referral perhaps the nutritional depletion of some of these patients was not appreciated by the referring physician.

What clinical, everyday parameters do you use in assessing the nutritional status of patients? Specifically, what parameters do you use to decide that a patient is nutritionally ready for operative intervention?

A last point worth emphasizing is the impressive figure of approximately 40% IVH induced remission, and approximately a 40% rate of non-operative fistula closure with intravenous hyperalimentation. And to echo Dr. Nance's question, I would ask you again: How long do you persist at the outside in continuing the IVH, in the hope of producing a non-operative remission? How long can one safely persist in this before deciding that surgery has to be embarked upon?

DR. ROBERT RYAN (New Orleans, Louisiana): We have found that hyperalimentation is quite necessary in the treatment of head and neck cancer patients with chemotherapy. (Slide) We previously have reported on the importance of sensitizing patients with topical 5-FU before using the drug intralesionally and intravenously. I would like to show a patient to illustrate the problem.

(Slide) The next slide is a summary on a 75-year-old Negro woman who came in, presented with a large submental abscess. This patient weighed 73 pounds. She had a huge cancer that filled the floor of the mouth, extended along the gutters on both sides beyond the angle of the mandible. The only surgical treatment that one would think of for curative purposes would be a total chin, tongue, larynx—complete Andy Gump—and certainly on a 75-year-old woman that weighed 73 pounds, this was out of the question.

This patient was hyperalimented for about three to four weeks. After two weeks we started in sensitizing her by applying 5% Efudex right on the lesion in the floor of the mouth, just smearing it on once a day. After another two weeks we then started to inject the lesion.

I'd like to show you her pictures taken just three weeks ago. (Slide) This is all that remains, with a little raw area on the mandible underneath the chin.

(Slide) And the next picture shows the floor of the mouth, and she is now essentially healed. She now weighs 115 pounds.

This work has recently been explained at the College of Surgeons meeting, and the last slide (slide) shows the work from the laboratory. We now have proof that hyperalimentation does speed up the antibody formation when one challenges the patient. Again, the lab has confirmed things that we as surgeons have known.

The hyperalimentation, I think, is one of our greatest advances, not only for treatment of bowel disease, but for many other areas; and we are just now starting to learn its importance in immune reactions. If you will, hyperalimentation is the crank that will start the motor.

DR. JONATHAN E. RHOADS (Philadelphia, Pennsylvania): Dr. Fitts has had a long and intense interest in inflammatory bowel disease, and a great many of the patients studied were patients referred to him and which he has followed.

My contribution, if any, to this was an insistence that we explore the positive side of nitrogen balance, and we got a start on this by a rather complicated technique of using diuretics, which permitted us to give five to seven liters of intravenous solutions per day. Dr. Harry Vars had used central venous administration in dogs, and, of course, a number of other people have done so in man—Dr. Clarence Dennis for one. Dr. Stanley Dudrick combined this with some very careful studies in dogs, and a suggestion of Aubaniac that the subclavian route be used (which made it possible to use a rather short catheter) and he deserves the credit for really pressing this forward with a group of colleagues and getting the method which we now use going.

There are a modest number of patients, as Dr. Rosato has mentioned, that have been admitted with the idea that they would require operation who have improved sufficiently on intravenous hyperalimentation so that so far they haven't had to be operated on, even though two or more years have gone by.

The recurrence rate in enteritis treated with surgical techniques is known to be high; how high depends on how it is measured. Bockus and Lee reported 90%, based largely on x-ray changes. When Dr. Philip Hodes and I made a study, we found that on a clinical basis it was much lower than this. But patients once having this disease, I presume, are never safe from it, so that one will never know just what the long-range cure rate is.

DR. W. CLARK HARGROVE (Closing discussion): In answer to Dr. Nance's questions, we were unable to determine from these data which patients would respond best to hyperalimentation. It was our general impression that in the granulomatous disease group it would be best used as primary therapy, and that in the ulcerative colitis patients it would be used more as an adjunct to therapy, although in certain ulcerative colitis patients we have seen a dramatic response with hyperalimentation alone.

As far as your question on the cost of hyperalimentation—with the cost of the hospitalization, plus the therapy, we estimate about $500 a day. So if that's a 26 day treatment, it's going to be close to $13,000.

We also want to emphasize that hyperalimentation is no substitute for the general principles of the treatment of fistulae. Distal obstruction must be relieved, excision of foreign bodies and epithelialized tracts must be done, and drainage of abscesses accomplished.

If there is complete disruption of the bowel, I don't think any of us can expect hyperalimentation to put it back together. Also with enterovesical fistulas, once the patient is stabilized and gotten into reasonable metabolic condition, he probably should be operated upon.

Dr. Rosato's question as to the immunological competence of these patients—this was a retrospective study, and immunological testing was not done. However, any patient now receiving hyperalimentation at our institution undergoes a nutritional assessment protocol of which skin test antigens is an integral part, and although we do some more sophisticated tests in certain groups of patients, we feel that the skin tests are our best clinical indication of the immune competence.

We continue hyperalimentation for about four weeks. If the fistula has not healed by this time, it's probably not going to heal with hyperalimentation alone, although in certain instances we have pushed to six weeks.

I'd like to thank Dr. Ryan for his comments, and I think all of us recognize the tremendous contribution Dr. Rhoads has made to the development of this treatment modality.

Comparison of the Results of Resection, Bypass, and Bypass with Exclusion for Ileocecal Crohn's Disease

WILLIAM P. HOMAN, M.D., PETER DINEEN, M.D.

From the Department of Surgery,
New York Hospital-Cornell Medical Center
New York, New York

Controversy continues regarding the optimal surgical treatment of Crohn's disease involving the ileum and cecum. Over 43-years, 161 patients underwent primary surgery for this disease at The New York Hospital-Cornell Medical Center. Resection was performed in 115 patients, bypass with exclusion in 25, and side-to-side ileotransverse colostomy in 21. Overall recurrence rates were 25% for resection, 63% for bypass with exclusion, and 75% for simple bypass. Expressed as 15 year follow-up, recurrence rates were 65% for resection, 82% for bypass with exclusion, and 94% for simple bypass. Much of the difference in final outcome was accounted for by early recurrence or by persistent disease in the two bypass groups. This amounted to 21% for the bypass with exclusion and 45% for simple bypass as compared to 3% for patients who had resection. Conclusions from this review are that 1) resection can be performed with a morbidity and mortality equivalent to either of the bypass procedures; 2) the recurrence rate following resection is significantly lower than bypass with exclusion or simple bypass, and amounts to about 4% per year; 3) continuing disease in the bypassed loop accounts for a high percentage of reoperations in the bypass groups, while appearance of new disease is the usual problem following resection; 4) resection is the surgical treatment of choice for ileocecal Crohn's disease.

THERE HAVE BEEN THREE generally accepted methods of dealing surgically with Crohn's disease of the ileocecal area: 1) simple bypass; 2) bypass with exclusion of the involved segment; and 3) resection. While there has been a trend toward resection as primary treatment in recent years, there still remains controversy over the choice of operation. This is especially true when bypass with exclusion is compared with resection.[2,15,16] Comparative studies either have lumped bypass with and without exclusion together, or have included only small numbers of patients who have had bypass with exclusion, which makes comparative evaluation difficult.[3,4,11] In addition, some studies report recurrence rates without adequately indicating length of follow-up, which casts a doubt on the comparability of the figures.

By reviewing the course of patients seen at The New York Hospital-Cornell Medical Center (NYH-CMC), we hoped to gain insight into the most reliable method of surgically treating ileocecal Crohn's disease.

Materials and Methods

To keep the number of variables to a minimum, this study was limited to patients in whom 1) Crohn's disease was confined to the ileocecal region, 2) the procedure under evaluation was the patient's first for Crohn's disease, and 3) the procedure was performed at NYH-CMC. Using these criteria there were 161 patients available for study from a total of 503 patients treated between 1932 and 1975.

Of the patients under study, 115 were treated by resection of the involved bowel, 25 by bypass with exclusion, and 21 by side to side ileotransverse colostomy (Figs. 1–3). The mean ages of patients undergoing these operations were 33, 30 and 34 years respectively. Follow-up data were obtained from the

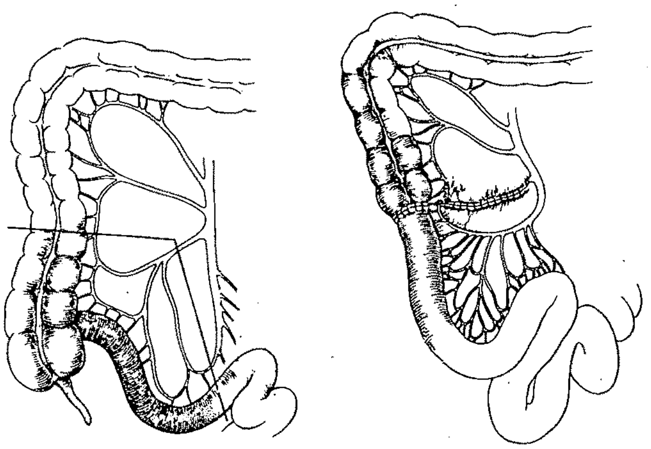


FIG. 1. Resection 115 patients—overall recurrence rate 25%.

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

0003-4932-78/0500-0530-0075 © J. B. Lippincott Company

patient's chart, from direct communication with the patient, or from his private physician. For the purposes of this review a follow-up was considered complete if a patient was followed until he had a recurrence requiring a second procedure, or if his status was known at the end of 1975 provided he had not required further surgery. Thus in the resection group of patients 13 (11%) had incomplete follow-up, while one patient each in the bypass with exclusion group (4%), and in the bypass in continuity group (5%) were incompletely followed.

Results

Differences in the results of surgical therapy for ileocecal Crohn's disease were marked and clearly favored resection as the therapy of choice.

Complications

The two deaths in this series both occurred in patients who had undergone resection, and each was the result of anastomotic dehiscence; the operative mortality rate in this group of patients was 1.7%. There was no mortality in either of the bypass groups. The complication rate was 6% in patients who had resection, 4% in patients who underwent bypass with exclusion, and 10% in patients who had simple bypass. Tabulation of complications is given in Table 1.

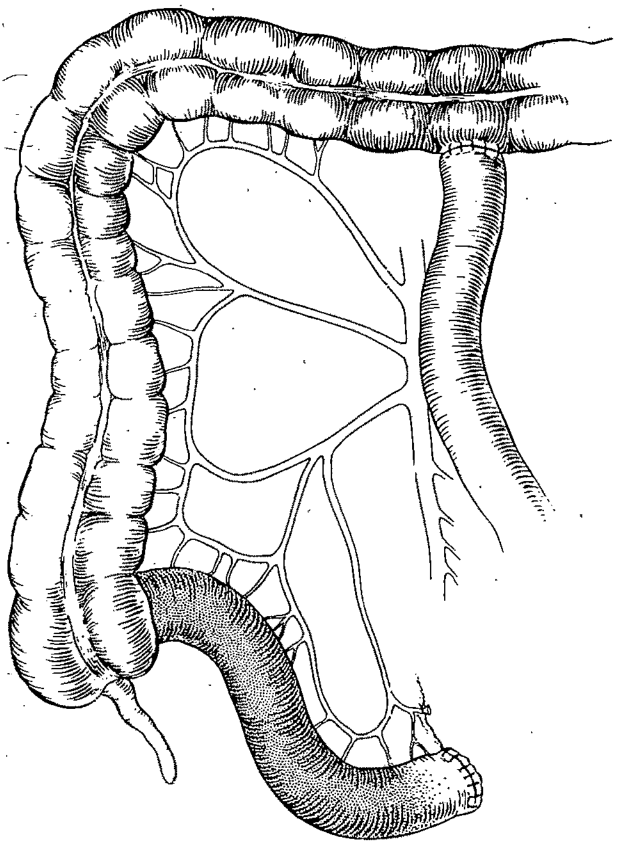


FIG. 2. Bypass with exclusion 25 patients—overall recurrence rate 63%.

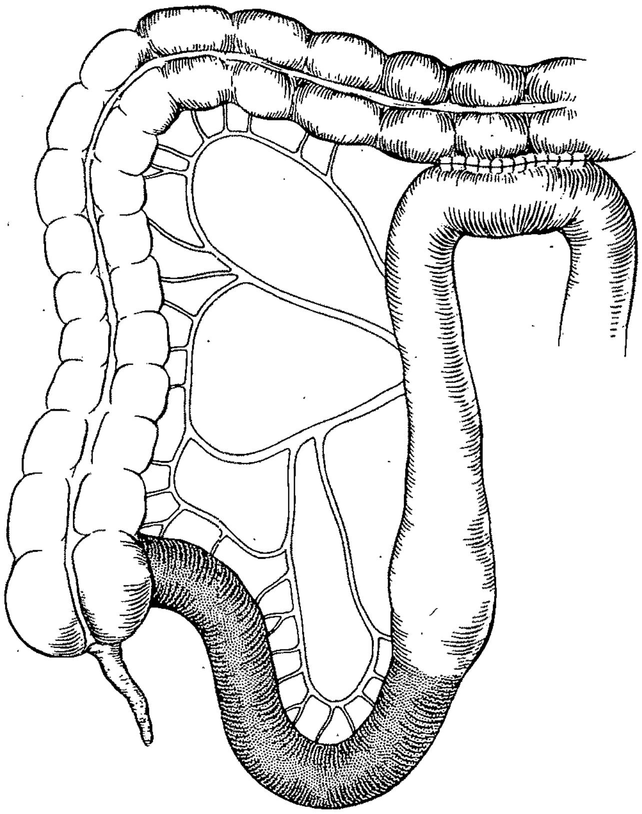


FIG. 3. Simple bypass 21 patients—overall recurrence rate 75%.

Recurrence Rates

Recurrence in Crohn's disease is notoriously difficult to define. In this study we have chosen to judge the lack of success of the primary operation by the need to perform a secondary operation to control either persistent or recurrent symptoms of disease. In patients who had originally undergone resection 25 patients required a second abdominal operation. This yields an overall recurrence rate of 25% among patients who received an adequate follow-up. There was an overall recurrence rate of 63% among patients having had bypass with exclusion, and of 75% among those having had bypass alone (Fig. 1–3).

An objection to comparing crude recurrence rates is that patients who had bypass operations had an opportunity for longer follow-up, since these operations were generally popular in the 1940's, and early 1950's.[3,11] Resection, on the other hand, only subsequently became popular, permitting a shorter follow-up. As an indication of this, in our series the median year of operation for resection was 1963, while the median years for bypass with exclusion, and for

TABLE 1. *Complications of Surgical Therapy*

Procedure	Complication	
Resection	Intra-abdominal abscess	(3 patients)
	Deep vein phlebitis	(1 patient)
	Bowel obstruction (adhesions)	(1 patient)
	Granylamatous peritonitis	(1 patient)
	Wound dehiscence	(1 patient)
		7 (6%)
Bypass with exclusion	Postoperative bleeding	(1 patient)
		1 (4%)
Bypass without exclusion	Wound infection	(1 patient)
	Ileocutaneous fistula	(1 patient)
		2 (10%)

bypass in continuity were 1948 and 1950 respectively. With a longer period of observation patients would theoretically have a greater chance of recurrence.

To circumvent this problem, recurrence rates have been calculated yearly based upon the cumulative number of reoperations required, and upon the number of patients whose status is known as of that year. For example, of 21 patients who had bypass without exclusion 15 patients, by five years, had required an additional procedure; two patients had not required reoperation, but were not followed for as long as five years. Thus the recurrence rate for patients at risk was 15/19, or 81%. Figure 4 gives a graphic representation comparing the recurrence rates for patients at risk following each of the three types of operation. From the curves it is interesting to observe that nearly all the difference in final outcome can be accounted for by the frequent necessity for reoperation within the first year in the bypass groups. Forty-five per cent of patients initially undergoing bypass without exclusion required reoperation within the first year postoperatively. Likewise a figure of 50% is given by Schofield.[14] On the other hand, figures of 21% and 3% apply to the bypass with exclusion group and to the resection group respectively. Of patients who were available for study 15 years following the original surgery, 65% of those originally having resection required reoperation, while comparative figures are 82% and 94% for the bypass with exclusion and simple bypass groups respectively. A marked superiority of resection is evident from the graph compared to either of the bypass groups. ($X^2 = 26.6$; df = 2; $p < 0.005$ at five years).

Reasons for Additional Surgical Treatment

Indications for reoperation are given in Table 2. Of note is the fact that 40% of patients who had simple bypass and 27% of patients who had bypass with exclusion required the second surgical procedure for continuance of the process which had necessitated the primary operation. None of the patients who had resection required reoperation for persistent disease. Thus, for reliability in satisfactorily *controlling the* disease resection is superior to bypass with exclusion which, in turn, is superior to simple bypass.

Are The Three Groups Comparable?

It is reasonable to question the validity of comparing these three groups of patients on the grounds that the indications for the operations may have been different, or that the bypass operations may have been reserved for the more difficult cases—the ones most likely to suffer recurrence. In fact, however, the indications for the primary surgery were nearly identical. This is shown in Table 3 where the percentage of patients requiring operation for a particular indication is comparable in each of the three groups.

Similarly, the operations compared in this study were performed sequentially with few exceptions. The bypass operations were performed primarily until the early 1950's, and resection operations were performed thereafter. Thus, the theoretic objection that results are skewed because the difficult patients were treated with a more limited operation may only apply when comparing the two bypass groups with one another, but not when comparing the resection group to either bypass group.

Another factor which could possibly have improved the results of resective therapy over bypass was the introduction of corticosteroids in the treatment of Crohn's disease. Only two patients (8%) in the bypass with exclusion group, and two (10%) in the bypass

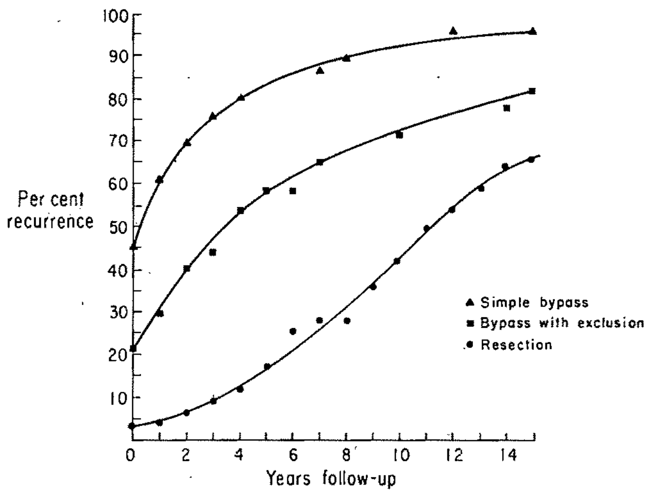


FIG. 4. Rate of recurrence of Crohn's Disease following surgical therapy.

TABLE 2. *Indications for Reoperation*

	Initial Operation		
Indication	Resection	Bypass with Exclusion	Bypass without Exclusion
Stenosis or recurrent inflammation	20 Patients (80%)	9 Patients (60%)	5 Patients (34%)
Continued disease	None	4 Patients (27%)	6 Patients (40%)
Fistula	5 Patients (20%)	2 Patients (13%)	4 Patients (27%)
Total	25 Patients (100%)	15 Patients (100%)	15 Patients (100%)

without exclusion group received corticosteroids. In contrast 26 patients (23%) undergoing resection received corticosteroids during the portion of their disease under study. Interestingly, patients receiving steroids within the group having resection actually fared considerably worse than patients who did not require steroids. This is probably due to patient selection (Fig. 5). Thus corticosteroids alone probably do not account for the differences between the bypass and resection procedures.

Discussion

Almost since the discovery of Crohn's disease as a specific disease entity in 1932, its proper surgical treatment has been the subject of lively debate. There was general agreement early in the history of the disease that the results of simple bypass were inferior to other forms of surgical therapy.[4,5,9] Therefore when President Eisenhower underwent a simple bypass procedure in 1956 a considerable furor arose.[10,13] Garlock and Crohn[9] in 1951 expressed their conviction that bypass with exclusion was superior to resection based upon a lower recurrence rate, and a decrease in mortality. Their experiences, however, were not shared by others, and by the end of the decade resection had become the treatment of choice in the minds of many experts.[7] Doubts have continued to remain over the superiority of resection to bypass with exclusion because definitive data are lacking.[15,16] Recognition that perforation,[1,17] carcinoma,[12] and persistent disease[6] may occur in the bypassed loop has lead to the adoption of resection by most surgeons. Similarly, restoration of flow through the excluded bowel is rarely possible, and was not performed in any patient in this series.

Alexander-Williams et al.[3] have reported their comparative results of resection and simple bypass for ileal Crohn's disease. At ten years their reoperation rates were of the order of 50% for resection and 90% for bypass. Similarly Koudahl et al.[11] reported rates of 56 and 72%. These latter authors, however, do not differentiate between the results of simple bypass and bypass with exclusion in their figures. In neither of these papers, therefore, is it possible to make a definite statement in regard to the results of resection versus bypass with exclusion. By contrast our figures at ten years are 41% for resection, 94% for simple bypass, and 71% for bypass with exclusion.

Our data further indicate that the recurrence rate following resection forms virtually a linear progression at about 4% per year with little or no levelling off after a 15 year follow-up. While a significant number of patients receive prolonged relief following resective surgery, one wonders if any patient would ever truly be cured after surgery given a long enough period of follow-up.

In addition, there is no evidence from our material that recurrences in ileocecal Crohn's disease tend to be biphasic, as indicated by deDombal et al.,[8] wherein new disease arises either in the first year or two after resection, or five to 15 years later. Apparently others[3,11]

TABLE 3. *Indication for Primary Surgery in Patients with Crohn's Disease*

Indication	Resection	Bypass with Exclusion	Bypass without Exclusion
Stenosis or intractability	72 Patients (63%)	17 Patients (68%)	13 Patients (62%)
Complication of perforation*	28 Patients (24%)	7 Patients (28%)	6 Patients (28%)
Other†	15 Patients (13%)	1 Patient (4%)	2 Patients (10%)
Total	115 Patients (100%)	25 Patients (100%)	21 Patients (100%)

* Fistula, abscess, acute perforation.

† Hemorrhage, hydronephrosis, acute abdominal pain.

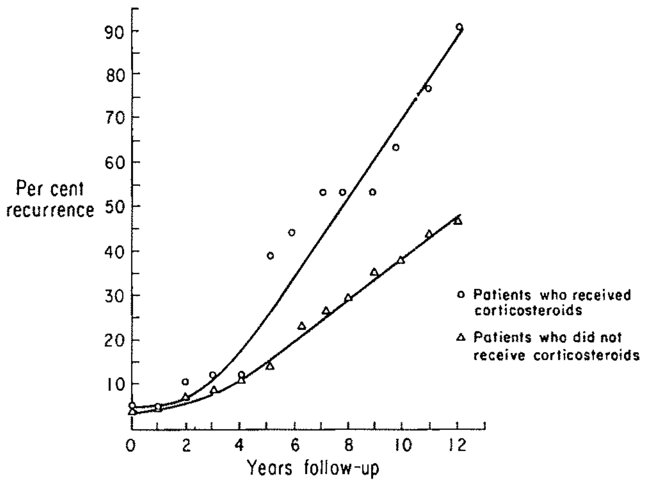


FIG. 5. Recurrence rate following resection in patients receiving and not receiving corticosteroids.

have not been able to demonstrate this tendency either. The reason for this discrepancy is conjectural, but we believe that recurrence in ileocecal Crohn's disease occurs linearly with time following resection if all gross disease is removed at the time of surgery.

Within the limits imposed by a retrospective study of this nature, we have shown that resection as initial surgical therapy in patients with ileocecal Crohn's disease can be performed with a morbidity and mortality equivalent to either of the bypass procedures. The recurrence rates for resection are far lower when compared either to bypass with exclusion or to simple bypass. Following bypass operations continuing disease in the bypassed loop accounts for a high percentage of reoperations, while following resection appearance of new disease is most often the problem. Resection is usually the procedure of choice for surgical treatment of ileocecal Crohn's disease.

On the other hand we feel that if resection would endanger normal structures because of extensive inflammation, or if resection would entail entering an abscess cavity, then bypass would be indicated—preferably bypass with exclusion. If this is chosen, and if distal obstruction is thought to be present, consideration should be given to venting the excluded bowel, either by tube enterostomy or by mucous fistula.

References

1. Alavi, I. A., Printen, K. and Steigmann, F.: Free Perforation in Chronic Regional Enteritis. Am. J. Dig. Dis., 14:420, 1969.
2. Alexander-Williams, J.: Progress Report: The Place of Surgery in Crohn's Disease. Gut, 12:739, 1971.
3. Alexander-Williams, J., Fielding, J. F. and Cooke, W. T.: A Comparison of Results of Excision and Bypass for Ileal Crohn's Disease. Gut, 13:973:974, 1972.
4. Atwell, J. D., Duthie, H. L. and Goligher, J. C.: The Outcome of Crohn's Disease. Br. J. Surg., 52:966, 1965.
5. Brown, C. H. and Daffner, J. E.: Regional Enteritis. II. Results of Medical and Surgical Treatment in 100 Patients. Ann. Int. Med., 49:595, 1958.
6. Colcock, B. P.: Operative Technique in Surgery for Crohn's Disease and its Relationship To Recurrence. Surg. Clin. North Am., 53:375, 1973.
7. Crohn, B. B.: Panel Discussion. Regional Enteritis. Gastroenterology, 36:398, 1959.
8. deDombal, F. T., Burton, I. and Goligher, J. C.: Recurrence Of Crohn's Disease After Primary Excisional Surgery. Gut, 12:519, 1971.
9. Garlock, J. H., Crohn, B. B., Klein, S. H. and Yarnis, H.: An Appraisal of the Long-Term Results of Surgical Treatment of Regional Ileitis. Gastroenterology, 19:414, 1951.
10. Heaton, L. D., Ravdin, I. S., Blades, B. and Whelan T. J.: President Eisenhower's Operation For Regional Enteritis. A Footnote To History. Ann. Surg., 159:661, 1964.
11. Koudahl, G., Kristensen, M. and Lenz, K.: Bypass Compared With Resection For Ileal Crohn's Disease. Scand. J. Gastroenterology, 9:203, 1974.
12. Nesbit, R. R., Jr., Elbadawi, N. A., Morton, J. and Cooper, R. A., Jr.: Carcinoma Of The Bowel: A Complication Of Regional Enteritis. Cancer, 37:2959, 1976.
13. Ravdin, I.: Discussion of Barber, K. W., Jr., Waugh, J. M., Beahrs, O. H. and Sauer W. G.: Indications for and the Results of the Surgical Treatment of Regional Enteritis. Ann. Surg. 156:472, 1962.
14. Schofield, P. F.: The Natural History and Treatment of Crohn's Disease. Ann. R. Coll. Surg. Engl., 36:258, 1965.
15. Spiro, H. M.: Clinical Gastroenterology. London, The MacMillan Company, 1970, p. 418.
16. Storer, E. H.: Small intestine, *In* Schwartz, S. I. (ed): Principles of Surgery. New York, McGraw-Hill Book Co., 1969, p. 943.
17. Waye, J. D. and Lithgow, C.: Small Bowel Perforation in Regional Enteritis. Gastroenterology, 53:629, 1967.

DISCUSSION

DR. JOHN H. BEAL (Chicago, Illinois): This is a unique review of the results of surgical treatment of Crohn's disease, because it covers a period of 43 years. The data presented should do much to settle the issue of which is the preferred operation for ileocecal Crohn's disease. The difference between resection and bypass, with or without exclusion, is striking.

It should be noted that Dr. Dineen has carefully selected a specific group of patients, those with Crohn's disease of the ileocecal region. His observations, obviously, will not hold for certain portions of the bowel where resection is usually not indicated, such as Crohn's disease involving the duodenum.

There are some minor criticisms that might be raised. There is one basic concern in the concept of recurrence among the patients that he has reported when resection is compared with bypass. After a bypass, the additional or recurrent inflammatory disease might be considered merely as extension of the process, rather than recurrence.

In addition, one might question whether the groups are truly comparable. There are factors influencing recurrence, such as age, or duration of the disease before operation, which have not been analyzed. However, it is doubtful that this could account for the differences between the groups.

Our experience tends to support Dr. Dineen's. Dr. Stuart Poticha of our institution has recently reviewed his series at the Northwestern Memorial Hospital, where resection has been accepted as the preferred treatment. Among 26 patients resected since 1968, only five recurrences, or 19%, have been encountered. This is not statistically different from the experience that Dr. Dineen presented, due to the numbers and the shorter length of follow-up.

The results for resection in the treatment of ileocecal Crohn's disease thus parallels in some ways the treatment of Crohn's disease of the colon, where the prognosis after colectomy and ileostomy is excellent.

I have enjoyed Dr. Dineen's presentation, and I think that this is a significant contribution to our understanding of the surgical treatment of Crohn's disease.

Dr. Robert Zeppa (Miami, Florida):

I'm sure that both would agree with me that a definitive answer could probably have been achieved if we had all embarked upon a prospective randomized cooperative study of these particular procedures. However, we are left with retrospective data in most of our institutions, and I must say this has been one of the most scholarly approaches to the utilization of such data; in particular, the application of a modified actuarial approach to look at the complication rates.

I had attempted to look at our institution's information, to see if we had anything comparable. The patients coming into the hospital average somewhere between 12 and 18 a year over the last several years, have all been operated on elsewhere, and so we have no *de novo* disease with which to compare our results.

My bias after reading this very scholarly presentation of Drs. Homan and Dineen is to agree with them that resection is the procedure of choice.

I have only one question for Dr. Dineen, and this is: What was the recurrence rate in those groups who required reoperation in the first year?

In fact, I would presume, although it's not clearly stated, that those patients who had bypass surgery then underwent resection, and it would be interesting to know whether the recurrence rate was higher than the actuarially discovered 4% per year for that group.

Dr. William P. Homan (Closing discussion): As far as Dr. Beal's comments, I agree with him that, especially in the bypass groups, the majority of the problem was in persistent disease, rather than in recurring disease, although for a study like this it becomes a matter of semantics, you know. When is it recurrence, or when is it persistent disease?

It's obviously impossible to be absolutely sure that these three groups are comparable, being a retrospective study. As far as we can tell, because these operations were performed sequentially, and also because the duration of the disease prior to operation was virtually the same in the three groups, about five years in each, we think that these three groups are comparable.

Dr. Zeppa asked about the recurrence rate in patients following their second operation. In most cases, these patients did undergo a resection, finally, and when we looked at this the recurrence rate was exactly the same, about 4% a year.

Another point I'd like to make is that we also discovered that the reoperation rate was not influenced by the duration of the disease prior to the resection; and this pretty much goes along with other studies on the subject.

One last point I'd like to mention is that when you read the literature, you see that people are saying, for example, "Although 25% of Crohn's disease patients have recurrence following resection, you actually cure 75% of the patients from the disease." But if you look at our graph, it appears that, if you follow the patients long enough, nobody will ever be cured, really. As an example of this, we even had a patient who went as long as 30 years following resection, who was totally asymptomatic, and finally had a recurrence of the disease and required another operation.

The Surgical Aspects of Chronic Mucosal Inflammatory Bowel Disease (Chronic Ulcerative Colitis)

JONATHAN A. VAN HEERDEN, M.B., F.R.C.S.(C), DONALD C. McILRATH, M.D., MARTIN A. ADSON, M.D.

From the Mayo Clinic and Mayo Foundation,
Rochester, Minnesota

The surgical aspects of chronic mucosal inflammatory bowel disease were reviewed by comparing the experience at our institution between two periods, one a decade later than the other (1961–1965 and 1971–1975). The striking findings were a marked decrease in the incidence of carcinoma and toxic megacolon and a marked increase in use of one-stage proctocolectomy with either Brooke ileostomy or Kock pouch. There was, in addition, a corresponding decrease in the operative mortality for elective cases, from 2.4 to 1.3%; yet the operative mortality for emergency cases remained relatively stable at about 25%. The reason for the decrease in the incidence of carcinoma and toxic megacolon appears to be on the basis of selection outside of our institution, in that fewer of these cases are being referred.

NONSPECIFIC INFLAMMATORY bowel disease occurs in two typical forms: transmural (Crohn's or granulomatous disease) and mucosal (chronic ulcerative colitis). The latter continues to be an enigma. The etiology is obscure, the manifestations diverse and poorly understood, and the medical treatment largely empiric. Surgical treatment is definitive and can well be curative. The timing of this intervention, the selection of the surgical procedure, and the care of these patients—often critically ill—require mature surgical judgment and expertise as well as a close relationship between medical and surgical disciplines.

Although much has been written regarding certain medical and pathologic aspects of chronic ulcerative colitis, the overall surgical approach and management are dealt with in relatively sparse publications,[4,5,7–9,11,12,17–19] including but few from the Mayo Clinic.[1,2,6,13,15] Consequently we undertook to assess, in a retrospective fashion, our past and current experience with this fascinating disease.

Materials and Methods

During the five years from 1961 through 1965, mucosal inflammatory bowel disease was indexed in 1,811 cases at our institution, and in 123 (7%) of them, the first surgery for the disorder was performed in our department. During the years 1971 through 1975, the same diagnosis was indexed in 1,658 cases and the first surgery for it was performed here in 226 (14%) of them. We reviewed these two groups and compared them with particular attention to any trends discernible between the earlier and later study periods.

Findings

Clinical Features

There was no significant difference of age or sex distribution between the periods studied (Table 1) and no statistical decrease in the interval from disease onset to operative intervention.

Among the earlier group, 42% (52 patients) had received steroids as a part of their medical management prior to operation, most of them on a long-term basis. Of the more recent group, 65% (148 patients) had received steroid treatment.

Indication for Operation

Surgical treatment of this disease was indicated essentially for the complications thereof (Table 2). These complications were either colonic or extra-colonic, at times multiple and subtle, and often categorized as failure of medical management (intractability).

Surgical Procedures

The procedure most often employed was one-stage proctocolectomy with conventional Brooke ileostomy. In the early 1970's the Kock pouch was coming in vogue, hence the increased incidence of this procedure in the latter group (Table 3). The incidence of ileorectostomies decreased from 12 to 4%, as seen. The miscellaneous procedures in the first group ranged from

---

Presented at the Annual meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests: J. A. van Heerden, M.D., Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55901.

Submitted for publication: December 8, 1977.

0003-4932-78-0500-0536-0075 © J. B. Lippincott Company

TABLE 1. *Preoperative Characteristics of Studied Groups with Chronic Ulcerative Colitis*

	1961–1965	1971–1975
All patients	123	226
Male	56	91
Female	67	135
Mean age, yr	39	36
Onset to operation, yr	9	9

bypass procedures to simple biopsies to ileostomies alone.

Short-Term Results

Emergency cases. In the first group, 30 cases (24%) were dealt with as emergencies—mainly for colonic perforation or toxic megacolon, or both. The interval from admission to operation in this group ranged from three to 102 days, averaging 18 days. The operative mortality in these cases was 8/30 (27%). Sepsis and shock were the main causes of death.

In the later group, 17 patients (8%) underwent emergency operation at 0–24 days after admission (5.4 days average). The operative mortality was 4/17 (24%); and all of the deaths were due to sepsis.

Elective cases. After elective surgery, the course of recovery was entirely uneventful in 63% of the first group and in 86% of the second. The corresponding operative mortality rates were 2.4% (three patients) and 1.3% (three patients), respectively. For the elective and emergency cases combined, the operative mortality rates were 8.9% (11 patients) in the 1960's group and 3.1% (7 patients) in the 1970's group.

Toxic megacolon. Of the 18 patients with toxic megacolon in the earlier group, three (17%) died in the immediate postoperative period. All three of them had undergone abdominal colectomy and ileostomy. Only one of the 18 had had one-stage proctocolectomy.

TABLE 2. *Indications for Operation in Chronic Ulcerative Colitis*

	1961–1965	1971–1975
	No. pts (% of 123)	No. pts (% of 226)
Colonic		
Toxic megacolon	18 (14)	15 (7)
Perforation	18 (15)	5 (2)
Carcinoma	28 (24)	12 (5)
Stricture	7	20
Massive hemorrhage	2	1
Extra-colonic		
General debility	48	154
Anemia	81	77
Hepatic dysfunction	11	17
Cutaneous	3	12
Ocular	2	1
Joints	3	18

TABLE 3. *Surgical Procedures Performed for Chronic Ulcerative Colitis*

	1961–1965	1971–1975
	No. pts (% of 123)	No. pts (% of 226)
Proctocolectomy		
Brooke ileostomy	56 } (46)	148 } (88)
Kock pouch	0	51
Abdominal colectomy and ileostomy	34	15
Ileorectostomy	15 (12)	10 (4)
Miscellaneous	18	2

In the later group there were 15 cases of toxic megacolon and three operative deaths among them (20%). The surgery in those 3 cases had been abdominal colectomy and ileostomy, but one-stage proctocolectomy had been performed in nine of the 15.

Long-Term Results

Complete follow-up was obtained in all 123 cases of our first group and in all but one of the 226 in our second group. The average lengths of follow-up were 10.5 and 3.6 years, respectively. The current status of the patients in each group is seen in Table 4 and the causes of death are in Table 5. The actuarial survival curves are shown in Figure 1.

Proctectomy was done after the primary surgery in 22 cases (33%) of the 1960's group and in 6 (8%) of the later group. The most common later operation required was revision of an ileostomy. This was done in 15 cases (12%) of the earlier group and in 66 (29%) of the second. In the latter group, revision was required 11 times among the 148 patients who had undergone Brooke ileostomy (incidence 7%) and 55 times among the 51 patients who had had Kock ileostomy. Of these 51, there were 21 who required no revision; but a small number required as many as six revisions of the nipple.

Age. Overall, there were 13 patients who were less than 20 years of age at the time of operation. Three (23%) of them died in the immediate postoperative period, but the other ten had excellent long-term results.

Ileorectostomy. The results of ileorectostomy are

TABLE 4. *Long-term Results (Current Status) After Surgical Treatment for Chronic Ulcerative Colitis*

	1961–1965	1971–1975
	No. pts (% of 123)	No. pts (% of 226)
Excellent	87 } (71)	209 } (93)
Fair	3	2
Dead	44	8
Total	134*	219

* Some patients with excellent long-term results died subsequently.

TABLE 5. *Cause of Late Death After Operation for Chronic Ulcerative Colitis*

	1961–1965 (123 pts)	1971–1975 (226 pts)
Carcinoma of colon	17	4
Carcinoma of bile ducts	3	0
Sepsis	11	1
Miscellaneous	13	3
Total	44	8

TABLE 6. *Results of Ileorectostomy for Chronic Ulcerative Colitis*

	1961–1965	1971–1975
Patients	15 (12% of 123)	10 (4% of 226)
Excellent result	4 (Average 13.3 years)	8 (Average 2.7 years)
Subsequent proctectomy	6 (Carcinoma of stump = 2)	2
Died	5 (Carcinoma bile ducts = 2) (Carcinoma colon = 1 (Unrelated = 2)	1 (Unrelated)

shown in Table 6. Worth noting is the decrease of the incidence of this procedure from one decade to the next (12–4%) and the fact that carcinoma occurred in the rectal stump in only two patients, both in the earlier group (13% of it).

Malignancy. During the 1961–1965 period, 28 patients were found to have carcinoma at the time of exploration. The five-year survival in this group was 39% (11 patients). In the more recent half decade, 12 patients with carcinoma were encountered, of whom 25% (three patients) survived five years.

Discussion

Many surgeons remember when surgical treatment for chronic ulcerative colitis was considered only after nonspecific medical therapy had been exhausted and the patient was desperately ill. This attitude, which was prevalent into the 1950's, developed not only because the risk of operation was formidable but also because many of the patients who survived operation were unable to resume a normal role in society.

During the past 20 years improvements in surgical care have altered favorably the outlook for these patients. No longer is it necessary for them to struggle with ill-fitting appliances, skin problems, and lack of guidance and support from fellow ostomates. Stomal therapists providing instruction in the use of modern appliances and skin care, and the benefits offered by organized ostomy groups have given the ostomate of today the opportunity to live a productive life without physical or social limitations. Such improvement in the postoperative status of patients occurred during the 10 years covered in this study (Fig. 1) and more than 90% of patients who underwent operation between 1971 and 1975 reported an excellent result (Table 4).

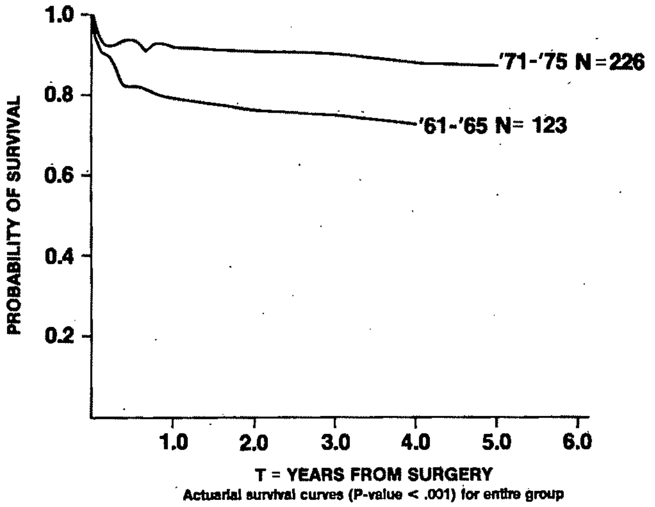


FIG. 1. Actuarial survival curves ($p < 0.001$) for the entire group.

The risk of surgical treatment has been reduced through the years. In this series, the overall operative mortality, including emergency cases, decreased from 8.9 to 3.1% during the ten years. Mortality in elective cases similarly decreased from 2.4 to 1.3%.

Because the risk of operation has been reduced and the quality of life with an ileostomy has been improved, opinion about when operation should be recommended has shifted steadily toward earlier surgical intervention. Decrease in average length of hospital stay before operation in emergency cases from 18 to 5.4 days and reduction in the percentage of emergency cases from 24 to 8% in the two groups of patients indicate that the trend toward earlier operation occurred in our practice between 1960 and 1970. This trend was reflected also in the increased percentage of patients with chronic ulcerative colitis who were treated surgically (7–13%).

Although the above-mentioned reduction of the overall rate of operative mortality was not aided appreciably by improvement among emergency cases (only from 27 to 24%), it does reflect the substantial lowering of the incidence of emergency treatment (24–8%). These data support the contention that initiation of surgical treatment given before the development of life-threatening complications (including perforation of the bowel, massive hemorrhage, and toxic megacolon) will reduce the operative risk.

It seems apparent also that operative intervention should occur before extra-colonic manifestations of chronic ulcerative colitis have taken a permanent toll. Ideally, no patient should suffer irreversible joint damage from arthritis or develop progressive hepatic dysfunction. Neither should children with the disease be retarded permanently in growth and development.

Colonic carcinoma remains a threat to all patients, and the risk of this complication increases with duration of disease.[10] Because the incidence of malignancy within ten years is known to be approximately 10%, one can logically recommend removal of the colon to avoid this hazard. The multicentricity, poor differentiation, and dismal prognosis of this carcinoma are well known; and our experience in this series has been distressing.

The reason for the decline in the incidence of carcinoma (and toxic megacolon) encountered eludes us, particularly since the interval from onset of symptoms to operation was identical in each group. In fact, the average duration of disease prior to the finding of colonic carcinomas was 15 and 17 years respectively in the two groups, precluding earlier diagnosis as a cause for this decline of incidence. It is possible that the referral practice has changed, in that more patients with carcinoma and toxic megacolon are being treated surgically by their local physicians, who have gained both experience and confidence in caring for such patients.

The primary reason for operative intervention is failure of the patient to thrive despite good medical care (Table 3). Recognition of this state is not difficult, but the tendency to procrastinate and delay operation is still too common. All too often, high-dose steroid treatment is prolonged, and its inevitable complications affect the operative risk adversely.

The choice of operative procedure is between proctocolectomy with ileostomy and abdominal colectomy with ileorectostomy. Results of preoperative proctoscopic examination are the prime factor in making the choice. The rectum-saving procedure should be reserved, in our opinion, for those patients who have no disease in the rectum. Only eight of the 226 (4%) patients operated upon between 1971 and 1975 underwent ileorectostomy. Six of the eight have an excellent result at 2.7 years average follow-up; the other two have undergone subsequent proctectomy.

Sometimes, for a patient who has a diseased rectum but also is critically ill, the surgeon resorts to an alternative procedure—colectomy and ileostomy with either closure of the rectum or establishment of a sigmoidal mucous fistula. The rectum is removed at a later date.

Although the procedure most commonly performed in both groups was one-stage proctocolectomy with conventional Brooke ileostomy (Table 3), 51 (26%) of the group with operation between 1970 and 1975 had an ileal reservoir (Kock pouch) rather than Brooke ileostomy. This subgroup required a disproportionate number of revisions (55 in the 51 patients with the pouch vs. 11—which is 7%—in the 148 patients with conventional ileostomy); and despite significant improvement in subsequent experience with the Kock pouch, the procedure still should be considered experimental.[3] The current rate of revision is approximately 25%.

When there is evidence of colonic malignancy, colectomy should be done in a way that provides wide en bloc resection of the mesentery and regional lymph nodes. When rectal cancer is present, proctectomy also should be done as widely as possible. In all other cases, removal of the rectum should be accomplished in the most conservative manner in order to reduce the chance of impotence to the lowest possible level. Other procedures included under the miscellaneous category (Table 3) (ileostomy without resection, multiple colotomies, *etc.*) are to be avoided.

When the colon is dilated massively, one may choose to decompass the bowel via a rectal tube or by suction on a large-bore needle inserted into the dilated segment. In many cases no attempt should be made to dissect the omentum from the transverse colon, because the omentum may be an integral part of the wall of the bowel.

When perforation of the colon has occurred, the peritoneal cavity should be lavaged thoroughly with saline solution or one containing antibiotics. Drains should be left where contamination was excessive.

Risk of postoperative infection has been reduced in our practice by the routine of irrigating with antibiotic solutions, for several days after operation, the catheters left in the subcutaneous space of the abdominal incision and in the presacral space.[14,16]

Comparison of results in patients who underwent operation for chronic ulcerative colitis in the periods 1960–1965 and 1970–1975 indicates improvement in surgical care during the ten-year interval. If the trend continues and basic surgical principles are applied, further progress in reduction in mortality and morbidity, elimination of irreversible extra-colonic complications, and overall improvement in long-term results can be expected. To ensure this trend, a close liason between medical and surgical disciplines is a sine quo non.

Acknowledgment

The preparation of this manuscript was facilitated by the expert help of Dr. L. Weiland (pathologist), Mr. D. Ilstrup (statistician) and Carol Kreter (secretary extraordinaire).

References

1. Akwari, O. E., van Heerden, J. A., Foulk, W. T. and Baggenstoss, A. H.: Cancer of the Bile Ducts Associated With Ulcerative Colitis. Ann. Surg., 181:303, 1975.

2. Bargen, J. A.: Chronic Ulcerative Colitis: Diagnostic and Therapeutic Problems; A Lifelong Study. Am. J. Roentgenol., 99:5, 1967.
3. Beahrs, O. H. and Adson, M. A.: Ileal Pouch With Ileostomy Rather Than Ileostomy Alone. Am. J. Surg., 125:154, 1973.
4. Binder, S. C., Miller, H. H. and Deterling, R. A., Jr.: Emergency and Urgent Operations for Ulcerative Colitis: The Procedure of Choice. Arch. Surg., 110:284, 1975.
5. Binder, S. C., Patterson, J. F. and Glotzer, D. J.: Toxic Megacolon in Ulcerative Colitis. Gastroenterology, 66:909, 1974.
6. Black, B. M.: Surgical Aspects of Chronic Inflammatory Diseases of Large Bowel. Am. Surg., 37:15, 1971.
7. Block, G. E., Moossa, A. R., Simonowitz, D. and Hassan, S. Z.: Emergency Colectomy for Inflammatory Bowel Disease. Surgery, 82:531, 1977.
8. Burt, C. A. V.: Surgical Management of Chronic Ulcerative Colitis. Dis. Colon Rectum, 8:323, 1965.
9. Crile, G., Jr.: The Treatment of Chronic Ulcerative Colitis. Gastroenterology, 54:817, 1968.
10. Devroede, G. J., Taylor, W. F., Sauer, W. G., et al.: Cancer Risk and Life Expectancy of Children With Ulcerative Colitis. N. Engl. J. Med., 285:17, 1971.
11. Goligher, J. C.: Treatment of Chronic Ulcerative Colitis. Curr. Probl. Surg., August 1965, pp. 1–38.
12. Goligher, J. C.: Surgical Aspects of Ulcerative Colitis and Crohn's Disease of the Large Bowel. Adv. Surg., 11:71, 1977.
13. Judd, E. S.: Surgical Progress in the Management of Chronic Ulcerative Colitis. Surgery, 60:783, 1966.
14. McIlrath, D. C., van Heerden, J. A., Edis, A. J., and Dozois, R. R.: Closure of Abdominal Incisions With Subcutaneous Catheters. Surgery, 80:411, 1976.
15. Odyniec, N. A., Judd, E. S. and Sauer, W. G.: Toxic Megacolon: Significant Improvement in Surgical Management. Arch. Surg., 94:638, 1967.
16. Schwab, P. M. and Kelly, K. A.: Primary Closure of the Perineal Wound After Proctectomy: A New Technique. Mayo Clin. Proc., 49:176, 1974.
17. Scott, H. W., Jr., Sawyers, J. L., Gobbel, W. G., Jr., et al.: Surgical Management of Toxic Dilatation of the Colon in Ulcerative Colitis. Ann. Surg., 179:647, 1974.
18. Thompson, J. C. and Villar, H. V.: Surgical Intervention in Chronic Ulcerative Colitis and Granulomatous Colitis. Am. Fam. Physician, 10:80, November 1974.
19. Veidenheimer, M. C. and Nugent, F. W.: Treatment of Chronic Ulcerative Colitis. Surg. Clin. North Am., 48:559, 1968.

DISCUSSION

DR. HUGH B. LYNN (Birmingham, Alabama): Most of the pediatric patients in this series were mine, and at least three of the deaths are on my conscience.

I'll confine my observations and carefully conceived and nurtured prejudices to the pediatric age group.

I'm really going to make a plea for a more aggressive approach in dealing with the pediatric age group. I should be talking to pediatricians and gastroenterologists, rather than surgeons. The actual choice of time for surgery depends on many factors. It's understandable that the parents are reluctant to subject their youngster to any form of surgery, but particularly to surgery which involves, in all probability, a permanent ileostomy. The family's reluctance, combined with the fact that a small but definite percentage of cases of ulcerative colitis in childhood will have a spontaneous remission with no recurrence, to the best of our knowledge, makes this decision even more difficult for the referring physician.

The surgeon's aggressiveness stems partially from his failure with advanced cases involving perforation, toxic megacolon, and malignant change, but his major stimulus to become aggressive comes from handling the actual pathology in the operating room, and recognizing that the extent of the disease far exceeds the x-ray and proctoscopic findings. The hopes for reversal or regression fade as he views the extent of the pathology.

The decision to operate is based on duration and severity of symptoms, the lack of response to medical management, and the attitude of the parents, the referring physician, and the patient. X-ray and proctoscopic findings, as well as the general physical state of the patient, all influence this decision. While it is often necessary to "sell" the operation to the family physician and the parents, it is remarkable how readily the children seem to accept the need for surgery, as well as the probability of a permanent ileostomy.

Communicating with another patient who has undergone similar surgery is frequently the most reassuring and convincing method of selling the necessary operation. Fathers of little girls are the most difficult to convince. I believe they secretly hope that surgery can be delayed until after the youngster grows up, marries, and comes home from the honeymoon. I have had one frustrated mother say, without her husband being present, "This little girl is never even going to discover boys, she's so busy looking for the escape hatch to the nearest ladies' room."

The choice of operation may include anything from an emergency ileostomy to a total proctocolectomy, and each operation has to be tailored to fit the degree of the emergency and the ability of the patient to withstand surgery. Operations of choice fall into two main categories; as Dr. van Heerden said, the total colectomy and proctocolectomy is the choice which we all favor. The subtotal colectomy or ileoproctostomy is the one the father always favors. At the present time, I have only one patient, to my knowledge, with ileoproctostomy, and that's because the father also has one, and they see a proctologist every three months together.

What I'm trying to say is that I am coming to believe that the earlier the onset of disease in a child, the shorter the period of medical treatment should be before surgery is undertaken. Follow-up care becomes a matter of not weeks or months, but of years. Once the surgeon has created an ileostomy, he has created a problem for his patient which he must help to control and solve over a period of many years. Turning a patient over to an ileostomy club or an appliance dealer may be easier for the surgeon, but it is not a fair surgical practice. Times are changing, and increased knowledge of the far-reaching effects of chronic ulcerative colitis when diagnosed in childhood must alter our thoughts on the surgical approach.

Reviewing these results leads me to conclude that steroids have created more risks in the treatment of chronic ulcerative colitis than they have eliminated. Frequently, necessary surgery has been delayed because of the glimmer of hope from a sense of well-being which the drug has produced, and at least three of my patients, in the words of Dr. Crile, "went smiling to the grave on cortisone."

Lastly, children can and do grow mature both physically and mentally while coping with a permanent ileostomy, and it is our impression that they adjust to this handicap better than adults, and enjoy the maturing experience of adolescence every bit as much as their more fortunate companions.

We believe that hyperalimentation should be in the hands of the surgeon, and this will convert the emergencies to elective operations. The first thing is to warn the family that the youngster is going to show much improvement under alimentation. We have gone almost completely to peripheral alimentation, using Intralipid and transfusion. We warn the family that the patient will become so much better that they will want to delay surgery.

I must say a word about the Kock pouch. It has not been used in any of my patients, for a couple of reasons. One is my lack of experience with it, though I am enthusiastic about the results in Dr. Beahrs' patients, and have talked to several of them, and Dr. Adson's also. In too many of the patients in my series the diagnosis has been in doubt, and I thought that Dr. Malcolm Dockerty and I were a minority of two who could not completely differentiate chronic ulcerative colitis from regional enteritis. I find that Dr. Fitts agrees with that.

We have explained the Kock pouch to the parents, and have explained that this will be available to them at a later date.

In closing, may I read just a letter, Dr. Scott, from a patient in this series, or from the parents of the patient, which I think illustrates many points. The referring physician and the father were strongly opposed to operating on this little nine-year-old girl.

> We are a family of four which has served four months now—lived four months with an ileostomy. We would like you to know what the operation has meant to this family. To my husband and me, as concerned and worried parents, it has meant our first nights of restful sleep in many, many months, and an end had come to our shuddering as we hear the running down the hall, the bathroom lights snap on, or later the tinkle of Tricia's call bell, when it becomes impossible for her to get to the bathroom quickly.
>
> It has been a job of seeing a face now pinkish, instead of the pallored gray, light up at the sight of a salad bowl, rather than that soft, bland diet she was used to.
>
> It's a joy of nine little girls playing statue maker on our front lawn, rather than one little girl standing alone, watching from the bedroom window the play activities of others on the warm spring afternoon.
>
> It is the comfort of seeing our daughter respond with normal growth and development pattern as she goes about her daily routine with renewed interest and zest.
>
> How much fun luncheons and bridge are now for my husband and me, and how we enjoy an evening out.
>
> Most important of all, for Patricia herself it has meant a new freedom—freedom from constant attention, constant trips to the doctor's office, with resulting hospitalization, freedom to resume the physical activities she loves so much, running and playing with other children and being in the swimming pool, chipping golf balls, planning an afternoon at the movies, whistling, singing, noisy activities in our household.
>
> As she goes about making plans for the future—and she has made quite a few—she is a different person. Surely she knows "There are so many children who have problems, and I don't consider that I have any handicap at all."

This is what makes the difference—surgery early in the youngster.

Dr. Oliver H. Beahrs (Rochester, Minnesota): Dr. van Heerden has indicated in his presentation the improvement of the surgical management of patients with ulcerative colitis over the years, and this becomes very important when we recognize that three or four decades ago the establishment of a conventional ileostomy was considered the exchange of one disease for another.

(Slide) With the use of a Brooke type of ileostomy there is considerable improvement over the experience with the older stem ileostomy. Revision of a Brooke ileostomy done for ulcerative colitis, granulomatous colitis, and noninflammatory disease is necessary in 10–20% of cases. However, 90% of these patients consider themselves to be in excellent health, compared to their previous condition, and are accepting usual avocational and vocational activities.

Now, as far as the continent ileostomy is concerned, the early experience was not good, in that about 50% required revision of the nipple valve or conversion to a nipple valve to establish continence. However. in the last 50 cases, 96% of cases at the time of discharge were continent and doing satisfactorily.

Revision of the nipple valve has been necessary in 26% of the patients sometime following creation of the pouch and ileostomy to re-establish continence. Twelve per cent have required two revisions or more. (Slide) In the total series of 107, when reviewed, 75% were in excellent condition, in that the pouch was continent, and 96% of the patients considered themselves to be in a much better condition than they were previously with the ulcerative colitis, or in a third of the patients, with a standard ileostomy which was converted to a continent ileostomy.

The continent ileostomy is a relatively new procedure and will continue to improve. It eliminates the need for wearing an external appliance. None of these patients have skin problems, and by properly selecting the patients, the mortality should be minimal. And, actually, in our experience to date in which 144 have been done, there has been no mortality.

Dr. van Heerden, I would put the alternatives the Kock pouch or the conventional ileostomy in that order rather than as you put it. Wouldn't you think it reasonable to give the patient some election as to which way he or she would like to go?

Dr. R. K. Gilchrist (Chicago, Illinois): I rise for one reason, and this is the future of the young woman who is to have this operation, and what is her family life?

About 12 years ago, I had 19 babies born to women that I had done total colectomies on. One had a placenta privia; all were otherwise uneventful, except for the one who got a small bowel obstruction, and the child was abnormal.

These people have very easy deliveries.

If you want your women to have babies, I would urge you to take three or four catgut stitches in the top of the uterus, and fix it to the most dependent part of this incision; because one of the reasons they have trouble with pregnancy or becoming pregnant is because the uterus falls back and becomes fixed in a retroverted position so they do not become pregnant.

One other point is the problem of persistent presacral fistula in these women, which happens occasionally.

When the scar in the back of the vagina becomes stiff, if you will simply make three or four incisions, posterior to the vaginal mucosa, freeing the scar, the woman simply takes her finger in the back of the vagina and massages it, and the vagina will drop right back into the space, and get rid of it.

The gynecologists complain of one other thing. They say that some of these women who have had their babies, have a little trouble with the retention of secretions in the most dependent part of this now backward-scooped vagina.

So that you can assure your young women that not only will they now look attractive—almost all of them have this beautiful complexion—and the boys just love them.

Dr. Jonathan A. van Heerden (Closing discussion): The emotional aspects of seeing ulcerative colitis in children, I think are frightening. I can remember vividly seeing some children who looked like they were nine, but who were actually 18, who were wearing diapers, who had ankylosing spondylitis, who were blind in one eye; and I'm sure Dr. Lynn knows the patients we are talking about.

I would certainly agree with Dr. Beahrs that patients should be presented all the alternatives, and the choice should be made by the patient and the physician.

Dr. Gilchrist, thank you for making some comments. You did mention the persistent perineal sinus. That is a problem to all of us. We have had less trouble in the past five or six years, since we have gone to the practice of, first, primarily closing the perineum; secondly, avoiding any silk sutures, using a subcuticular closure; and thirdly, putting two large Silastic catheters into the presacral space and irrigating this space for a full nine days.

(Slide) Dr. White, sitting next to me, unprovoked, asked me this question: Is the occurrence of carcinoma after ileorectostomy high enough to avoid this operation? I just happen to have a slide.

In 1961 through 1965, 12% had this operation. Four of the 15 had excellent results for an average follow-up of 13 years. Six patients required subsequent proctectomy, and carcinoma was encountered in the stump in two of the six. Five died, two of carcinoma of the bile ducts, one of carcinoma of the colon.

In the later series ten patients had this operation, and eight of the ten had excellent long-term follow-up, but it was shorter than in the earlier series. Two required subsequent proctectomy, and in neither one was carcinoma encountered in the stump.

Urinary Tract Complications with Rectal Surgery

JOHN R. BEAHRS, M.D., OLIVER H. BEAHRS, M.D., MARGARET M. BEAHRS, M.D., FRANK J. LEARY, M.D.

The possibility of urinary tract injury should always be considered in the course of anterior resection or combined abdominoperineal resection of the lower colon and rectum. Controlled studies of ureteral and other injuries and fistulas cannot be made; but fortunately, unanticipated damage to the lower urinary tract does not occur often. The surgeon operating in the pelvis should be aware of the problems rarely encountered and should be capable of their management. If a urologic surgeon is available, consultation often is desirable. Prompt intraoperative recognition is most important so remedial procedures can be carried out immediately. Delay in recognition and treatment jeopardizes the patient's course and the function of the urinary tract. Postoperative urinary tract infections should be diagnosed early so prompt treatment can be instituted.

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota

SIGNIFICANT URINARY TRACT COMPLICATIONS continue to occur infrequently in the course of rectal surgery or during the immediate postoperative period. Some complications arise from the disease process (malignant or inflammatory) but those are not to be considered in this report unless the definitive surgical treatment requires manipulation or removal of a segment of the lower urinary tract. Iatrogenic injury of the ureters, bladder, or urethra should be rare, since the surgeon should be constantly aware of these structures in the course of the surgical procedure. Even so, and especially in patients who have had previous surgery, accidental injury to tissue can occur, since gross identification sometimes is nearly impossible because of scarring or the recurrent pathologic process. In such cases identification can be attempted by looking for the structure (ureter) away from the pathologic site and tracing it into the area of pathology. But once again, further identification may be impossible because of the tissue reaction which is present.

As pointed out by Symmonds,[7] controlled studies of ureteral injuries and fistulas cannot be made; so discussion of their etiology and management must consist of personal experience and opinion. This is as true for surgery of the lower colon and rectum as it is in gynecologic surgery. Likewise, the incidence of urinary complications is difficult to determine with validity because of the many and varied factors present in any series of cases. A previous study by Vandertoll and Beahrs[8] revealed urinary retention in 68 (4%) of 1,766 patients who underwent surgical procedures on the rectum. Thirty-three of these patients had to accept transurethral resection for relief of obstructive symptoms during the postoperative period. Wilson and Beahrs[10] reported that significant urinary tract infections occurred after operation in 3.8% of 902 patients undergoing anterior resection, and minor urinary infections were somewhat more frequent. Major urinary tract problems, mostly ureteral, occur about once a year on the surgical service of O.H.B. where approximately 165 colon and rectal cases are done.

Although the general surgeons should have close liaison with the urologic and gynecologic surgeons, expert advice and consultation is not always immediately available during an operation. Therefore, the surgeon working in the pelvis should be prepared by training and experience to deal with any problem that might arise with the urinary tract and to restore its continuity if interrupted. Similarly, postoperative complications of urinary tract retention and infection must be recognized and properly managed, either on the service of the surgeon or by referral to the appropriate specialist.

Case Reports

Problems encountered intraoperatively in rectal surgery and postoperatively with the urinary tract are best related by review of several illustrative cases.

Case 1. A 64-year-old man was admitted to the hospital for recurrent carcinoma of the lower sigmoid colon. Resection of splenic flexure, descending colon, sigmoid, and rectosigmoid was carried out and a transverse colorectostomy (end-to-end) was then performed. Removal of the sigmoid and rectosigmoid from the hollow

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint address: J. R. Beahrs, M.D., c/o Section of Publications, Mayo Clinic, 200 First Street SW, Rochester, MN 55901.

Submitted for publication: December 8, 1977.

0003-4932-78-0500-0542-0085 © J. B. Lippincott Company

of the sacrum and left lateral pelvic wall was difficult because of scarring. The left ureter was identified and carefully dissected from the colon, to which it was attached by scar tissue. Two Penrose drains were left in the hollow of the sacrum and brought out through a stab wound lateral to the incision. The postoperative course was complicated by urinary retention that necessitated transurethral resection of the prostate. Six weeks after the abdominal surgery, the patient returned with a left ureterocutaneous fistula through the stab wound site. The fistula was demonstrated by sodium indigotindisulfonate (indigo carmine) given intravenously. An excretory urogram showed marked delayed secretion on the left, with hydronephrosis. The right kidney was normal. Presumably the blood supply to the ureter had been interrupted, leading to necrosis of a segment of it. A left nephrectomy and partial ureterectomy was performed.

Case 2. A 65-year-old woman with a diagnosis of diverticulitis with abscess underwent abdominal exploration and resection of a portion of the sigmoid and a portion of the rectum including an old anastomosis. Intestinal continuity was reestablished by sigmoidorectostomy (end-to-end). In the process of freeing the lower sigmoid and a rectosigmoid, dense scar tissue secondary to the disease process and previous operation was encountered. The bowel was freed with some difficulty from the pelvic wall; and in the process of delivering this portion of the bowel from the pelvis, the left ureter was torn. It was embedded in dense scar tissue immediately adjacent to the ovary. The bladder was opened and a no. 5 ureteral catheter was inserted through the ureteral orifice and advanced through the ureter, past the defect, and into the ureter above the defect, almost to the renal pelvis. The ureter was reapproximated with five sutures of 4-0 catgut. The catheter was brought out through the suprapubic portion of the bladder and the defect in the bladder was closed. The ureterotomy site was drained.

Case 3. A 75-year-old woman was operated on for a large cancer of the lower descending colon. A segment of the left ureter was inadvertently included in the resected specimen, and this was recognized on inspection of the operative site. A preoperative excretory urogram had not been obtained. Indigo carmine (5 ml) was given intravenously; and the dye escaped with urine from the bladder, indicating that the right kidney was functioning. Because of the age of the patient, extent of the cancer, and presence of other medical conditions, a decision was made for acute ligation of the left ureter proximal to the site of injury. The patient's recovery was uncomplicated, and subsequent evaluation of urinary tract function revealed a normal right kidney.

Case 4. A 50-year-old man presented with enterocolic cutaneous fistulas—a complication of a subtotal colectomy done elsewhere for diverticulitis. In a secondary operation, the multiple fistulas between the small intestine and colon and the skin were excised. Dense adhesions were present. At the primary operation the right colon had been anastomosed to the upper rectum, and the fistulous tracts were in the area of the pelvis. During the dissection, part of the right ureter was sacrificed, since it was embedded in scar tissue. The length of the right ureter would not allow reestablishment of its continuity, and therefore it was reimplanted into the mobile dome of the bladder with interrupted 4-0 chromic catgut as a ureteroneocystostomy. The bladder was secured with 2-0 chromic catgut to the posterior fascial layer of the pelvis at the site of reimplantation to relieve any possible tension on the ureteroneocystostomy. A no. 5 ureteral catheter was left in the right ureter and a no. 4 in the left ureter. Both were brought out suprapubically with a 16-F cystostomy tube through the dome of the bladder and the lower abdominal midline. The left ureteral stent was removed on the ninth postoperative day, the right ureteral stent on the twelfth day, the suprapubic tube on the seventeenth day, and the urethral catheter on the twentieth day. When seen seven months after surgery, the patient was able to void well and the excretory urogram was normal.

Case 5. A 51-year-old man who had primary carcinoma of the rectum with extension into adjacent tissues and regional metastasis underwent a combined abdominoperineal resection that necessitated bilateral seminal vesiculectomy and partial prostectomy.

Postoperatively, urine drained from the perineal wound. A urethral catheter was reinserted and left in place for four weeks. A retrograde urethrogram at the time of removal of the catheter outlined a 2.5 cm cavity below and communicating with the distal prostatic urethra. The perineal wound was healed. Cystoscopy revealed an opening, 3–4 mm in diameter, to the left of the base of the verumontanum. A urinoma developed which required drainage and subsequently excision of the urethroperineal fistula.

Case 6. A 75-year-old obese woman had had a sigmoid resection four years previously for diverticulitis. Six months ago she again had noted pain in the left lower quadrant of the abdomen, change in bowel habit (diarrhea), and, shortly afterward, pneumaturia. Evaluation confirmed the presence of a sigmoid vesical fistula. At a secondary operation it was seen that a loop of terminal ileum and the sigmoid colon at the site of the previous sigmoidosigmoidostomy were involved in an inflammatory mass with the base of the bladder, and a fistula connected all three structures. The operative procedure involved resection of a loop of ileum, resection of the sigmoid colon, and separation of the inflammatory mass from the bladder. The defect in the bladder, measuring 1 cm in diameter, was not resected but was merely closed with a single figure eight suture of catgut. Suction drainage of the bladder was used for one week. Recovery was uneventful.

Case 7. A 34-year-old woman with active chronic ulcerative colitis underwent total proctocolectomy with creation of an ileal reservoir and continent ileostomy. Preoperatively there were no symptoms from the urinary tract and results of urinalysis were normal. A urinary catheter was placed immediately before surgery and removed on the first postoperative day, the patient voiding well. A culture of the urine was negative. On the ninth postoperative day the patient complained of dysuria and urgency, and her temperature, taken orally, was 39.4°C. Cultures of the blood, rectal wound, and urine were obtained. The patient was treated empirically with ampicillin, 500 mg by mouth four times daily, and the urinary symptoms resolved. Urine culture was reported to show *Escherichia coli* $> 10^5$/ml, sensitive to ampicillin. Not surprisingly, the rectal wound also grew *E. coli* as well as various other organisms. This case is exemplary in two respects from the standpoint of postoperative infections of the urinary tract: 1) *E. coli* is the most frequent pathogen, and 2) the female with a rectal wound is at high risk for urethral contamination by contiguous spread.

Discussion

The first consideration in performance of surgery on the lower colon and rectum is adequate exposure of the anatomy that is to be dealt with. To work through small or ill-placed incisions so the "result" will be cosmetically pleasing is only to invite disaster. The pelvic anatomy should be known without question to the surgeon. The ureter should always be identified by inspection and the familiar snap on palpation. Unless the patient is obese, the ureters usually can be seen through the overlying parietal peritoneum. If they cannot be identified as they pass over the pelvic brim, dissection into the area from above should be

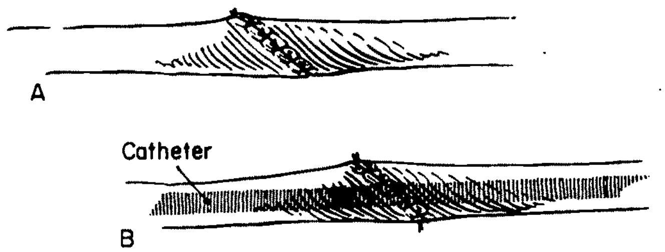


FIG. 1. (A) When ureter has been damaged or segment has been removed, if ends will come together without tension, end-to-end anastomosis can be made, using catgut sutures. The anastomosis should be oblique, to ensure adequacy of lumen. (B) Frequently, a ureteral catheter is inserted through anastomosis to serve as stent.

carried out until they are found. Peristaltic activity in the ureter, when seen, aids in confirmation. Care should always be taken not to strip adjacent tissue in such a manner as to interfere with the blood supply. Once each ureter is identified, one may hope to trace it distally if necessary, so that it is preserved in removing the pathologic tissue. The possibility of ureteral duplication must be kept in mind in the course of the dissection.

Excretory urography is desirable in cases considered preoperatively to be complicated. In uncomplicated cases, if kidney function is normal, that test is not required. However, it will alert the surgeon to abnormalities—deviation or obstruction of the ureter and ptosis of the kidney. But even though the ureters have been identified by x-ray, they must be seen physically at operation.

It has been considered desirable to insert ureteral catheters preoperatively; but this procedure is not always effective in avoiding injury (as noted by Higgins[3]), and to perform it in all cases hardly seems practical. Nevertheless, in selected cases it should be considered. During the operation, if it seems desirable to insert catheters into the ureters, when this has not been done preoperatively, the bladder can be opened extraperitoneally, the trigone identified, and a ureteral catheter inserted through the ureteral orifice proximally and distally out the urethra, and the bladder then can be closed.

In some patients who have had ureteral injury, the functional status of the kidneys is unknown. This information is needed for proper decision as to the management. A satisfactory method for making this determination intraoperatively is to give 5 ml of indigo carmine (sodium indigotindisulfonate; Hynson, Westcott and Dunning) intravenously and observe the outflow from the injured ureter as well as that from the bladder—either through a cystotomy opening or out the urethral catheter. With the knowledge that the opposite urinary tract is intact and functioning, the injured ureter may be ligated or nephrectomy done if deemed desirable, Intraoperative excretory urography could be considered.

If in the course of dissection of the pathologic tissue the ureter is seen to have been clamped, the site should be observed carefully for evidence of viability. If viable, then it would be reasonable to stent the ureter *with* a catheter for 5–7 days. This can be inserted by means of anterior cystotomy. As mentioned above, a catheter is inserted into the ureter and carefully passed until it splints the damaged area. The distal end then is passed readily through the urethral catheter, or it can be brought out suprapubically. Generally, small longitudinal or needle-like puncture wounds of the ureter can be managed with drainage alone.

If a short segment of ureter has been devitalized, then the procedure of choice would be resection of the devitalized portion and ureteroureterostomy by an end-to-end spatulated oblique anastomosis using 5-0 chromic catgut (Fig. 1). The Z-plasty technique described by DeWeerd and Henry[2] is useful when there is significant disparity in size between the ends. Ureteroneocystostomy becomes the procedure of choice when simple end-to-end reconstruction of a ureter cannot be accomplished. The length of ureteral segment removed, its level in the pelvis, and the ease with which extra mobility of ureter and bladder can be obtained will determine the surgeon's choice of ureteral repair. Previous surgery, pelvic pathology, and irradiation are additional determining factors.

When the ureter has been divided below the midpelvis, ureteroneocystostomy may be the simplest method of restoring its continuity. Extra length and mobility to ensure against tension on an anastomosis can be obtained by freeing up the proximal ureter. Additional length may be gained by reflecting the colon medially and then carefully mobilizing downward the upper ureter and kidney itself.

The bladder may be mobilized from the retropubic region. A bladder flap procedure also may be performed

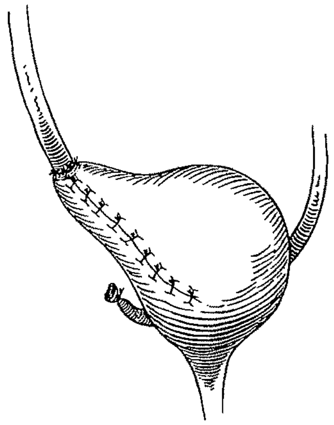


FIG. 2. If ureter and bladder cannot be brought together, a bladder flap can help to bridge gap. Parietal peritoneum can be used to reduce tension on and cover anastomosis.

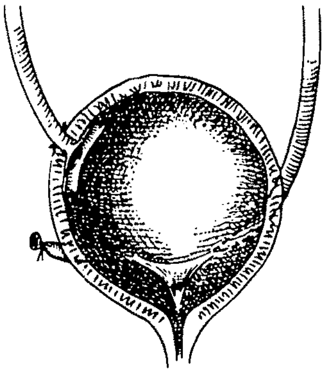


FIG. 3. When proximal ureter will not reach distal ureter but does approximate bladder, ureteroneocystostomy can join it to mobile dome of bladder. Ureter is fishmouthed, which prevents stricture.

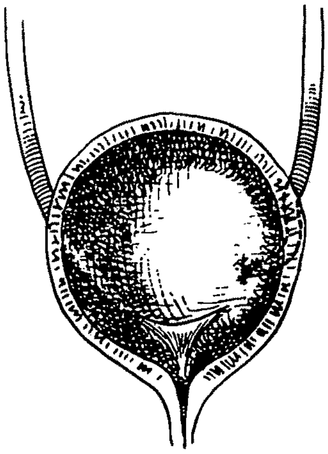


FIG. 4. When ureteroneocystostomy is done, ureter is brought obliquely through bladder wall and through submucosal tunnel to prevent reflux.

where large ureteral segments have been removed (Fig. 2).

The closed technique of ureteroneocystostomy can be performed quickly, but it is often followed by urinary reflux (Fig. 3).

Politano and Leadbetter[6] have described the submucosal tunneling technique for reimplantation of the ureter without complication of reflux (Fig. 4). This somewhat more time-consuming technique should be employed when the patient's condition and prognosis allow for increased operating time.

Transureteroureterostomy can be performed when significant destruction to the distal ureter has occurred (Fig. 5). The ureter is freed and brought across, below or above the inferior mesenteric artery and anterior to the great vessels, to the opposite ureter. Contraindications for this procedure (to avoid the possibility of an obstructed "common" ureter) include reflux and renal disease on the intact side and significant stone disease or history of stone disease. Interrupted 5-0 or 6-0 chromic suture is used and the region is drained through the retroperitoneum.

Ureterosigmoidostomy is best performed after adequate bowel preparation. Establishment of an ileal conduit and ureterosigmoidostomy are good forms of delayed urinary diversion. However, both require preoperative planning and both should be discussed with the patient before the operation.

Cutaneous ureterostomy can be performed when the above methods are not feasible or when the patient's condition or prognosis precludes extensive reconstruction. A catheter ureterostomy may be the safest and quickest procedure. Ileal segment replacement of the ureter and also autotransplantation are procedures that could be considered as secondary future reconstructive possibilities.

Ligation of the ureter may be performed safely when other reconstructive methods are not feasible, if the contralateral kidney is known to have normal function. When there has been no previous obstruction and no infection exists, acute ligation of the ureter will cause the kidney to cease function and atrophy asymptomatically.

When the urethra has been interrupted or partially resected in the course of the operative procedure, it should be repaired or prolonged urethral catheter drainage should be used to prevent leakage through the perineal wound or formation of a urinoma. If a stricture should later develop, it can be treated secondarily.

When an acute defect has been made in the bladder, two-layer closure with catgut suture is appropriate. Vesical drainage is included for about ten days. If a chronic defect is present, such as an enterovesical fistula, it is important not to resect the defect but merely to "freshen" the edges and close it with absorbable suture material. Suction drainage should be used to keep the bladder completely free of distention for a period of seven to ten days. Inflammation and scar-

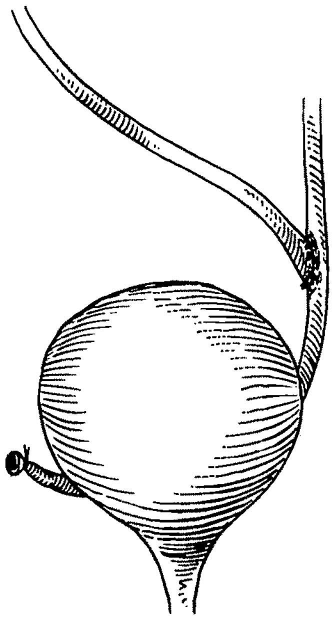


FIG. 5. If proximal ureter will not reach distal ureter or bladder, end-to-side transureteroureterostomy can be performed if there is no pathology and kidney function on contralateral side is normal.

ring of the bladder wall often requires removal of a major segment of bladder so that normal tissues can be used for closure.

Postoperative urinary retention is more common in men than women. In men retention occurs more often when preoperative symptoms of prostatism are marked. However, about 20% of patients with postoperative urinary retention deny any preoperative symptoms. The size of the prostate on rectal examination does not correlate with postoperative urinary retention.

If urinary tract obstruction occurs in male patients after major rectal surgery, intermittent or continuous catheter drainage may be necessary for days to weeks.

Conservative treatment for postoperative retention can be sufficient 70% of the time.[1] It consists of catheter drainage for varying periods, followed by intermittent catheterization until little or no residual urine remains. Other therapy includes management of infection and vesical stimulants. Urecholine seldom is helpful in resolving the problem. Transurethral resection is indicated if satisfactory voiding is not established by two to three weeks postoperatively.

The morbidity of postoperative urinary tract infections retards the patient's postoperative course and prolongs the hospital stay. Fortunately today, with multiple antibacterial agents, these can be well controlled, especially if recognized early. The incidence of postoperative urinary tract infection in a recent series of rectal surgery patients was 3.8%.[10] Predisposing factors which may be identified in the preanesthesia medical evaluation include urologic abnormalities (*i.e.*, vesicoureteral reflux, significant prostatic hypertrophy, renal calculi) and medical conditions that alter the host defense mechanisms in the urinary tract, such as diabetes mellitus, gout, chronic potassium deficiency, nephrocalcinosis, hypertension, and sickle cell disease.[4] Preoperative urinary tract infections should be identified and dealt with appropriately before surgery.

The surgical patient is likely to require urinary catheterization at some point during the hospital stay. Aseptic technique must attend the insertion, and a closed drainage system should be employed. Even so, bacterial colonization of the urine will occur in time in virtually all patients. Therefore the urinary catheter should be removed as soon as possible. Prophylactic antibiotic bowel preparation for intestinal surgery is routine at the Mayo Clinic: neomycin, 500 mg four times daily, and oxytetracycline (Terramycin), 250 mg four times daily, are given for 48 hours prior to surgery, in addition to the mechanical preparation of the bowel. Washington et al.[9] demonstrated a decreased postoperative incidence of wound and urinary tract infections with this regimen.

The suspicion of postoperative urinary tract infection is commonly raised by the patient's complaint of lower urinary irritative symptoms, the finding of pyuria on urinalysis, or the diagnostic work-up of postoperative fever. A significant urinary tract infection is diagnosed if a clean-catch, midstream urine sample contains $>10^5$ organisms per milliliter. During the wait for the results of culture and sensitivity testing, empiric antibiotic treatment is indicated. The most common infecting organism is *E. coli*, followed by *Proteus* sp., *Streptococcus faecalis, Pseudomonas* sp., and *Klebsiella*. For uncomplicated lower urinary tract infections, a sulfonamide or trimethoprim-sulfamethoxazole is the agent of first choice, followed by nitrofurantoin or nalidixic acid for patients unable to tolerate sulfonamides.[5] A course of seven to ten days is sufficient. Febrile urinary tract infections call for parenteral therapy with drugs that attain higher tissue levels, such as ampicillin or cephalothin. For the more tenacious organisms, aminoglycosides are often necessary, and treatment should continue 14 days. Antibiotics should be adjusted to accord with the sensitivity reports and for choice of the most specific, least toxic agent possible. Follow-up urine cultures in one month are indicated.

The possibility of urinary tract injury should always be considered in the course of anterior resection or combined abdominoperineal resection of the lower colon and rectum. The best treatment is avoidance; but if such injury occurs, prompt intraoperative recognition is most important so that remedial procedures can be carried out immediately. Delay in recognition and treatment jeopardizes the patient's course and the function of the urinary tract. Postoperative bladder and urinary tract infections should be diagnosed early so prompt treatment can be instituted.

References

1. Cook, E. N., Ten Cate, H. W. and Potter, W. M.: Urinary Retention Following Operations on the Bowel. J. Urol., 89:255, 1963.
2. DeWeerd, J. H. and Henry, J. D.: Z-Plastic Ureterouretero-stomy. J. Urol., 93:690, 1965.
3. Higgins, C. C.: Ureteral Injuries During Surgery: A Review of 87 Cases. JAMA, 199:82, 1967.
4. Kaye, D.: Host Defense Mechanisms in the Urinary Tract. Urol. Clin. North Am., 2:407, 1975.
5. Keys, T. F.: Antimicrobials Commonly Used for Urinary Tract Infection: Sulfonamides, Trimethoprim-Sulfamethoxazole, Nitrofurantoin, Nalidixic Acid. Mayo Clin. Proc., 52:680, 1977.
6. Politano, V. A. and Leadbetter, W. F.: An Operative Technique for the Correction of Vesicoureteral Reflux. J. Urol., 79:932, 1958.
7. Symmonds, R. E.: Ureteral Injuries Associated With Gynecologic Surgery: Prevention and Management. Clin. Obstet. Gynecol., 19:623, 1976.
8. Vandertoll, D. J. and Beahrs, O. H.: Carcinoma of Rectum

and Low Sigmoid: Evaluation of Anterior Resection of 1,766 Favorable Lesions. Arch. Surg., 90:793, 1965.

9. Washington, J. A. II, Dearing, W. H., Judd, E. S. and Elveback, L. R.: Effect of Preoperative Antibiotic Regimen on Development of Infection After Intestinal Surgery: Prospective, Randomized, Double-Blind Study. Ann. Surg., 180: 567, 1974.

10. Wilson, S. M. and Beahrs, O. H.: The Curative Treatment of Carcinoma of the Sigmoid, Rectosigmoid, and Rectum. Ann. Surg., 183:556, 1976.

Discussion

Dr. Scott Jones (Durham, North Carolina): These expertly and imaginatively managed cases illustrate clearly the principles of proper management of urinary tract complications occurring during surgery of the pelvic colon.

One fact which stands out in most patients sustaining intraoperative injuries is that most patients have had a previous, usually complicated, operation. I certainly agree with the authors that such patients should be evaluated preoperatively, with excretory urography and additional studies when indicated.

Although most urinary problems are related to the disease, or scarring, an occasional patient will have a urinary tract anomaly which may predispose to injury or other problems. (Slide) This is a case of crossed renal ectopia, demonstrated by retrograde urogram; but, of course, other abnormalities such as duplicated ureter, absent kidney, bladder diverticulum, and so forth, may cause problems.

Regarding retrograde ureteral catheterization, we believe that this procedure should be done preoperatively in patients having multiple previous complicated pelvic operations, radiation therapy, or large pelvic masses. Incidentally, the urologists now have available fiberoptic ureteral catheters which can be inserted preoperatively to permit intraoperative identification of the ureters, not only by palpation, but by transillumination as well.

The following case illustrates the utility of having ureteral catheters present preoperatively. (Slide) This is an x-ray of a patient, a 33-year-old woman, who had a thrill palpable on pelvic exam during pregnancy two years ago. Last year, because of pelvic fullness and dyspareunia, she was studied, found to have a pelvic AV malformation, and underwent ligation of her right hypogastric artery. Recently, because of recurrence of her symptoms, she was referred to Dr. David Sabiston, and this study was obtained, revealing surgical changes in the pelvis.

(Slide) The next slide shows the kidneys, ureter, and a huge pelvic AV malformation. Notice the passage of the right ureter through the operative site and the AVM. The presence of a ureteral catheter greatly facilitated the safe mobilization of the ureter from the scar and the AVM.

I have one question of the presenters. Have you had experience with urinary tract injuries which were not recognized intraoperatively? What clinical signs make you suspect a urinary tract injury in the postoperative period, and how do you proceed in such a circumstance?

Dr. Elgin W. Ware, Jr. (Dallas, Texas): I think that the various areas of concern could be summarized under the five headings of ureteral injury, bladder injury, injury to the urethra, and the postoperative complications of retention and infection.

The various techniques of dealing with ureteral injuries were covered quite adequately by Dr. Beahrs. I would simply emphasize the fundamentals that we are all taught in medical school, and which all of you know; and those are that any reanastomosis or anastomosis should be performed without tension, absorbable suture materials should be used, and the area should be adequately drained. We don't routinely use stents.

I don't think I could add to Dr. Beahrs' comments on treatment of ureteral injury, but I would like to point out the fact that preoperative intravenous pyelography is of inestimable value in these cases and should be performed routinely. Not only does it give us a rough idea of function of both sides of the upper tract, if both sides in fact, are present, but it also, in these litigious days that Dr. Scott referred to in his Presidential Address, gives us an idea about any pre-existing disease that might be present. Furthermore, in the complicated cases that Dr. Beahrs described, many of these being second and third operative procedures, I would think it would provide you fellows valuable information concerning any deviation from the normal course, or obstruction to, the ureter itself.

Lastly, from the urologic standpoint, in the male patient the I.V.P. gives us an idea about how much, if any, obstructive prostatism exists, if a postvoiding film is done. A rather rough estimate of residual urine is obtained, but it does prove valuable, not only in prognosis, but also in helping to decide how to deal with persistent postoperative retention, if such should occur.

In this same context I would like to say that we like to do a rectal examination on these people before surgery, because not all cases of obstructing prostatism can be dealt with transurethrally. If the prostate is quite large, than an open surgical technique has to be used.

I would like to ask Dr. Beahrs if he has had any experience while doing an abdominoperineal resection in removing perineally an obstructing benign prostatic adenoma at the time of the primary surgery, or having a urologic consultant do so.

Lastly, by way of historic interest, I would like to point out that the first planned nephrectomy was done by Professor Simon in France, I think the year was about 1876, and this was done for a persistent ureterocutaneous fistula that occurred as a result of a GYN operation of some type, in which the ureter was injured. Dr. Simon later removed the kidney. Although nephrectomies had been done inadvertently prior to that time for removal of masses thought to be ovarian, this was the first planned in advance.

I couldn't help but notice when I came into the hotel a plaque commemorating the one-hundredth anniversary meeting of the American Gynecologic Association which was held here in 1976, which I presume means that the founding of the American GYN Society was in 1876. I don't know whether this malhappening that was corrected by Dr. Simon had anything to do with that fact or not, but at least, in point of time, it occurred about the same year.

Dr. William L. Weems (Jackson, Mississippi): The authors of this paper only had time to touch on a few of the peaks in this big subject of discussion, and there really isn't time for those of us who wish to make comments to touch on many of the important aspects of the problem. To mention a few: the management of the various fistulas and strictures which might occur at various levels in the urinary tract; the use of urinary diversions as a preliminary measure, or as an adjuvant to the repair of injuries; to stent or not to stent, and if so how; the work that's being done in search for ureteral substitutes.

Our experience with ureteral injuries in 86 cases over about a ten year period showed that 22% of injuries are due to external violence. Seventy-eight per cent are surgically induced.

Now, that pretty much follows the percentages that one will find in the literature. Fifty-nine per cent of the total number of injuries were due to gynecological procedures, and 12% were incurred in the performance of general surgical operations; so that in terms of the magnitude of the problem, ureteral injuries are predominantly a gynecological surgical problem. All of us who operate in the pelvis must be alert to these possibilities, however.

(Slide) There are two important determinants of management in ureteral injuries: that is, the level of the injury and the presence or absence of loss of length. The most difficult repairs are in those cases in which there is significant loss of length. There are procedures available to us to compensate for this rather serious defect, and I would like to just briefly show pictures of those.

The bladder flap ureteroneocystostomy is a useful procedure in compensating for loss of ureteral length in the lower one-third of the ureter. Now, in general, when the ureter is injured in the lower one-third, it's better to put the ureter into the bladder than it is to reanastomose the ends of the ureter, because the success rate in ureteroneocystostomy far exceeds the success rate from primary ureteral anastomosis.

The bladder flap allows us to compensate for loss of length in the lower one-third. A more difficult problem is when there is loss of length in the middle one-third of the ureter. In recent years, the popularity of transureteroureterostomy has been much increased. There are some complications of this operation. Obviously, one subjects a normal renal unit to some risk; and yet, from a practical standpoint in carefully selected cases, this operation is easy to do and free of complications, and gets one out of a difficult situation with a minimum of morbidity and risk.

(Slide) This is a patient who sustained resection of the distal third of the ureter in the performance of an oophorectomy. An attempt was made to do a primary repair, and that failed. The second operation was done as an emergency because of pelvic sepsis, and the surgeon "bailed out" by bringing the ureter to the skin. This skin ureterostomy worked for several months, and we saw the patient at that stage. A transureteroureterostomy was not too difficult to do, and afforded a good result, as evidenced by this x-ray three months later.

An even more difficult problem is loss of length in the upper one-third of the ureter, where one does not have length enough to reach to the opposite member. There are a number of ways to compensate for that. One, of course, is nephrectomy; but I believe that in most patients who have a good prognosis from the standpoint of their age and other medical considerations, an effort to salvage a kidney probably is advisable.

Since there's no prosthetic substitute for the ureter that's workable, there are two viable options here, and one is the use of a bowel substitute for the ureter—an ileal replacement for the ureter—and probably that surgery should not be done except when the kidney is at a premium; in other words, when there is disease in the opposite kidney.

An autotransplant is a rarely indicated procedure, but when it is indicated, it's entirely feasible, and should give a good long-term result. (Slide) This is a patient with a self-inflicted gunshot injury that was not recognized until three or four weeks postinjury. This shows hydronephrosis, and a large collection of urine in the retroperitoneum on the excretory urogram.

The retrograde pyelogram shows the ureter ending blind here, and there was a defect that could not be bridged by mobilizing the kidney. An autotransplantation was done on this patient, and this is an IVP some six months after his injury.

One of the common, perplexing problems is that of bladder dysfunction after pelvic surgery. It's a common experience after difficult deliveries or hysterectomies, or any kind of pelvic surgery, for the bladder not to work very well for a few days. The reason for that is not too well recognized, but probably is a neurological phenomenon that may involve the autonomic nervous system. The simple explanation of paralysis or damage to the parasympathetics probably is not an adequate explanation, but vesicourethral dyssynergia with imbalance in the autonomic control of the bladder probably is an explanation.

In these patients one can only manage the condition in a palliative fashion, and hope that the neurological function will return. And that will occur in the great majority of patients. But an important point I'd like to make to you is that this damage can be aggravated and extended by permitting the bladder to become overdistended in the postoperative period. It has been recognized that the bladder can be damaged from overdistension, and one should protect against that in managing the patient in the postoperative period. Intermittent catheterization, rather than indwelling catheter drainage, is the procedure of choice.

Dr. Charles Eckert (Albany, New York): Dr. Beahrs has covered this subject completely, and his coverage has been added to by the previous discussants. Nevertheless, I have three points to make.

The first is, in these days of quality assurance programs and medical audits, we all have had to define patterns of acceptable preoperative care. For patients undergoing operations on the left colon and rectum, preoperative intravenous pyelography is certainly an essential.

The second: for primary anastomoses of the ureter, a number of years ago we had the temerity to give a paper before this group on the use of nonabsorbable suture material. If 6.0 or 7.0 vascular sutures are used, healing will be perfectly normal, with reepithelialization, and no evidence of calculus formation.

Finally, when the ureter is ligated, and the kidney is not removed, usually nothing bad will happen. However, if the patient has unsuspected pyelonephritis, ligation of the ureter may result in pyonephrosis. If the urine shows signs of infection, it is better to carry out nephroureterectomy than to simply ligate the ureter.

Dr. John R. Beahrs (Closing discussion): I would like to thank Dr. Jones, Dr. Ware, Dr. Weems, and Dr. Eckert for their excellent discussions. I can just briefly comment on some of the things they have said, and do appreciate the excellent questions they have raised.

Dr. Jones, in answer to your question of delayed urinary tract injuries and how they present, we divide complications into early and late postoperative complications. One of our cases, number 1, deals with a late complication.

Early complications can present with increased drainage from the abdominal wound, from the abdominal drains, per vagina or through the perineal wound or drains. Flank pain that persists or increases in intensity, an increasing mass in the abdomen, or anuria are all things that can signal trouble in the early postoperative period.

Quick and early diagnosis will lead to the most satisfactory outcome. A diagnosis of a urine leak can be made by checking a creatinine on the drainage and the serum simultaneously. Indigo carmine or methylene blue can be given and a diagnosis made if the drainage becomes colored.

Excretory urography can be done and it may help localize the injury. A urologist will usually become involved at that time and a cystoscopy and ureteral catheter can be placed or retrograde studies done depending on the situation.

Reexploration may become necessary. Nephrostomy can be done in the case of ligation of the ureter, if you are trying to save the kidney, and a nephrectomy may be inevitable if the trouble persists.

Thank you for bringing up the question about ureteral catheters. A ureteral catheter may be of help in facilitating the identification of the ureter, but it's only a tool, and has its limitations. It can be inconvenient in the preoperative or early anesthesia to transfer the patient from the cystoscopic area to the open room. The cost is a factor that must be kept in mind. It gives the physician a false sense of security when entering the pelvis. The pathology may render the catheters useless.

It should be kept in mind that at the time of operation a cystotomy can be performed. The ureteral orifices can be identified using methylene blue or indigo carmine, and catheters can be placed at that time if necessary.

Dr. Ware, thank you for your comments. The preoperative evaluation of prostatism is a very important point. A good history can usually give a clue as to whether the patient may have trouble in the postoperative period.

Excretory urography is also an important preoperative planning tool. It can provide important information regarding relationships of the ureters to the pelvic structures; double ureters can be noted, pelvic kidney, ureteral obstruction, and intrinsic disease. However, cost of the test is significant and it should be ordered only if the information is needed. This, again, is a tool, and it certainly does not facilitate ureteral identification at the operating table, and should be a surgeon's choice as to whether it's used.

Dr. Weems, we certainly thank you for your interesting case studies, and also alluding to the complicated problems that can develop and Dr. Eckert, thank you for your appropriate comments.

People need vitamins every day when they are healthy. Do they need them less when they are sick?

Patients receiving IV feeding need fat- and water-soluble vitamins every day. Adequate stores of fat-soluble vitamins should not be taken for granted.

M.V.I.® – *the only major multivitamin for infusion that supplies both water-soluble and fat-soluble vitamins in one preparation**

*Vitamin K, vitamin B_{12} and folic acid are optional additions to parenteral nutrition programs.

In IV feeding...

M.V.I.® **EVERY DAY**

(Multi-Vitamin Infusion)

The most comprehensive major parenteral multivitamin product

Each 10 cc. ampul† or 5 cc. Concentrate vial†† provides:

Ascorbic acid (C)	500 mg.
Vitamin A*	10,000 I.U.
Vitamin D* (ergocalciferol)	1,000 I.U.
Thiamine HCl (B_1)	50 mg.
Riboflavin (B_2)**	10 mg.
Pyridoxine HCl (B_6)	15 mg.
Niacinamide	100 mg.
Dexpanthenol	25 mg.
Vitamin E* (dl-alpha tocopheryl acetate)	5 I.U.

†With sorethytan laurate 1%, sodium hydroxide 1%, butylated hydroxytoluene 0.003%, butylated hydroxyanisole 0.0008%; and gentisic acid ethanolamide 2% as preservative.

††With propylene glycol 30% and gentisic acid ethanolamide 2% as stabilizers and preservatives, sodium hydroxide for pH adjustment, sorethytan laurate 1.6%, butylated hydroxytoluene 0.006%, butylated hydroxyanisole 0.0015%.

*Oil-soluble vitamins A, D and E water solubilized with sorethytan laurate.

*In Concentrate as riboflavin-5-phosphate.

PRODUCT INFORMATION

INDICATIONS: *in emergency feedings*– Surgery, extensive burns, fractures and other trauma, severe infectious diseases, comatose states, etc. may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. As a result, wound healing may be impaired, enzyme activity disturbed, hematopoietic tissues affected; hypoproteinemia and edema may appear; convalescence is thus prolonged.

In such patients M.V.I. (administered in intravenous fluids under proper dilution) contributes optimum vitamin intake toward maintaining the body's normal resistance and repair processes.

DIRECTIONS FOR USE: M.V.I. is ready for immediate use when added to intravenous infusion fluids.

For intravenous feeding, one daily dose of 10 cc. of M.V.I. or 5 cc. of M.V.I. Concentrate added directly to not less than 500 cc., preferably 1,000 cc., of intravenous dextrose, saline or similar infusion solutions...plasma, protein hydrolysates, etc.

PRECAUTION: Allergic reaction has been known to occur following intravenous administration of solutions containing thiamine.

CAUTION: Not to be given as a direct undiluted intravenous injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be discontinued as early as practical in favor of an intramuscular or oral vitamin preparation, if deemed advisable.

HOW SUPPLIED: M.V.I.—10 cc. ampuls, boxes of 25 and 100 (NSN 6505-00-455-9955/NSN 6505-00-424-9808A).

M.V.I. CONCENTRATE—5 cc. vials, boxes of 25. Available in 100s only (NSN 6505-00-212-6156A).

USV LABORATORIES

USV Laboratories, Division
USV Pharmaceutical Corp.
Tuckahoe, N.Y. 10707

Ready when you need it.

10 mg.
(2 ml.=10 mg.)
NDC 0007-0C51-01
1 Disposable Syringe with sterile 22 gauge, 1-1/4 inch needle
Compazine® Injection (2 ml.=10 mg.)
brand of prochlorperazine
For deep I.M. or I.V. administration
Do not use entire contents for children –
See dosage instructions
Bend back to open
10 mg.
(2 ml.=10 mg.)
LOT 153
EXP: 5/7

'Compazine' controls vomiting.

- Unsurpassed antiemetic action
- 12 dosage forms and strengths

NOTE: Do not use 'Compazine' in pediatric surgery. Not recommended for children under 20 lbs. or 2 years of age. In children with acute illnesses or dehydration, use only under close supervision.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: To control severe nausea and vomiting. For the management of the manifestations of psychotic disorders.

Possibly effective: To control excessive anxiety, tension and agitation as seen in neuroses or associated with somatic conditions.

'Compazine' has not been shown effective in the management of behavioral complications in patients with mental retardation.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings: The extrapyramidal symptoms which can occur secondary to 'Compazine' may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of 'Compazine' and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: The antiemetic action of 'Compazine' may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (See WARNINGS). Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. **In children with acute illnesses or dehydration, use only under close supervision.**

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

Supplied: Tablets—5, 10 and 25 mg., in bottles of 100; Spansule® capsules—10, 15, 30 and 75 mg., in bottles of 50; Injection—5 mg./ml. in 2 ml. ampuls, 10 ml. vials, and 2 ml. disposable syringes; Suppositories—2-1/2, 5 and 25 mg.; Syrup—5 mg./5 ml.; Concentrate (intended for institutional use only)—10 mg./ml.; Single Unit Packages of 100 (intended for institutional use only)—5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

Compazine® brand of **prochlorperazine** Injection: 5 mg./ml.

the emesis nemesis

SK&F
a SmithKline company

Smith Kline &French Laboratories Philadelphia, PA

ETHICON DOES IT AGAIN

VICRYL* (Polyglactin 910) suture

Improved braided construction results in:

Superior smoothness
Better knot security
Improved handling characteristics
—In addition to the other benefits VICRYL suture is known for. Available dyed and undyed on a wide variety of needles.

Available braided, dyed and undyed.

ETHICON
the closing word

*Trademark

(See next page for complete product information.)

© ETHICON, INC. 1978

Revised 6/77

VICRYL* (Polyglactin 910) suture

COMPLETE PRODUCT INFORMATION

**VICRYL* (Polyglactin 910)
Synthetic Absorbable Suture**

DESCRIPTION VICRYL (polyglactin 910) synthetic absorbable suture is prepared from a copolymer of glycolide and lactide. These substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$

VICRYL sutures are sterile, inert, nonantigenic, nonpyrogenic, and elicit only a mild tissue reaction during absorption. The braided and monofilament sutures are colored violet to enhance visibility in tissue. The braided suture is also available undyed (natural).

ACTIONS Two important characteristics describe the *in vivo* behavior of absorbable sutures: first, tensile strength retention, and second, the absorption rate (loss of mass).

Subcutaneous tissue implantation studies of VICRYL suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of VICRYL suture is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days

INDICATIONS VICRYL synthetic absorbable suture is intended for use as an absorbable suture or ligature.

CONTRAINDICATIONS This suture, being absorbable, should not be used where extended approximation of tissues under stress is required.

WARNINGS The safety and effectiveness of VICRYL (polyglactin 910) suture in neural tissue, and in cardiovascular surgery have not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize.

PRECAUTIONS VICRYL suture knots must be properly placed to be secure. Place the first throw in precise position for the final knot, using a double loop; tie the second throw square, using horizontal tension; additional throws are advisable

Skin and conjunctival sutures remaining in place longer than 7 days may cause localized irritation and should be removed as indicated.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds

ADVERSE REACTIONS Reactions reported in clinical trials which may have been suture related have been minimal. These include skin redness and induration, rare instances of hemorrhage, anastomotic leakage, wound separation in the eye, and abscesses

DOSAGE AND ADMINISTRATION Use as required per operation

HOW SUPPLIED VICRYL sutures are available sterile, as braided dyed (violet) and undyed (natural) strands in sizes 3 to 8-0, in a variety of lengths, with and without needles, and on LIGAPAK® ligating reels. VICRYL sutures, monofilament, dyed (violet) are available in sizes 9-0 and 10-0, in a variety of lengths with needles.

Also available in sizes 1 to 4-0 attached to
CONTROL RELEASE® needles

*Trademark

ETHICON

RADIOLOGICAL ASSAYS DIVERSIFIED

Announces Price Breakthrough
in

**CEA TESTING—
$14.00/ASSAY**

**VOLUME DISCOUNT AVAILABLE
DAILY ASSAY
ABNORMAL RESULTS PHONED**

For further information and
plasma mailers:

CALL (914) 592-6408

RADIOLOGICAL ASSAYS DIVERSIFIED
10 West Main Street
Elmsford, New York 10523

CHANGE OF ADDRESS

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the *Journal.*

Send Change of Address cards to:

**ANNALS OF SURGERY
c/o Fulfillment Manager
East Washington Square
Philadelphia, Penna. 19105**

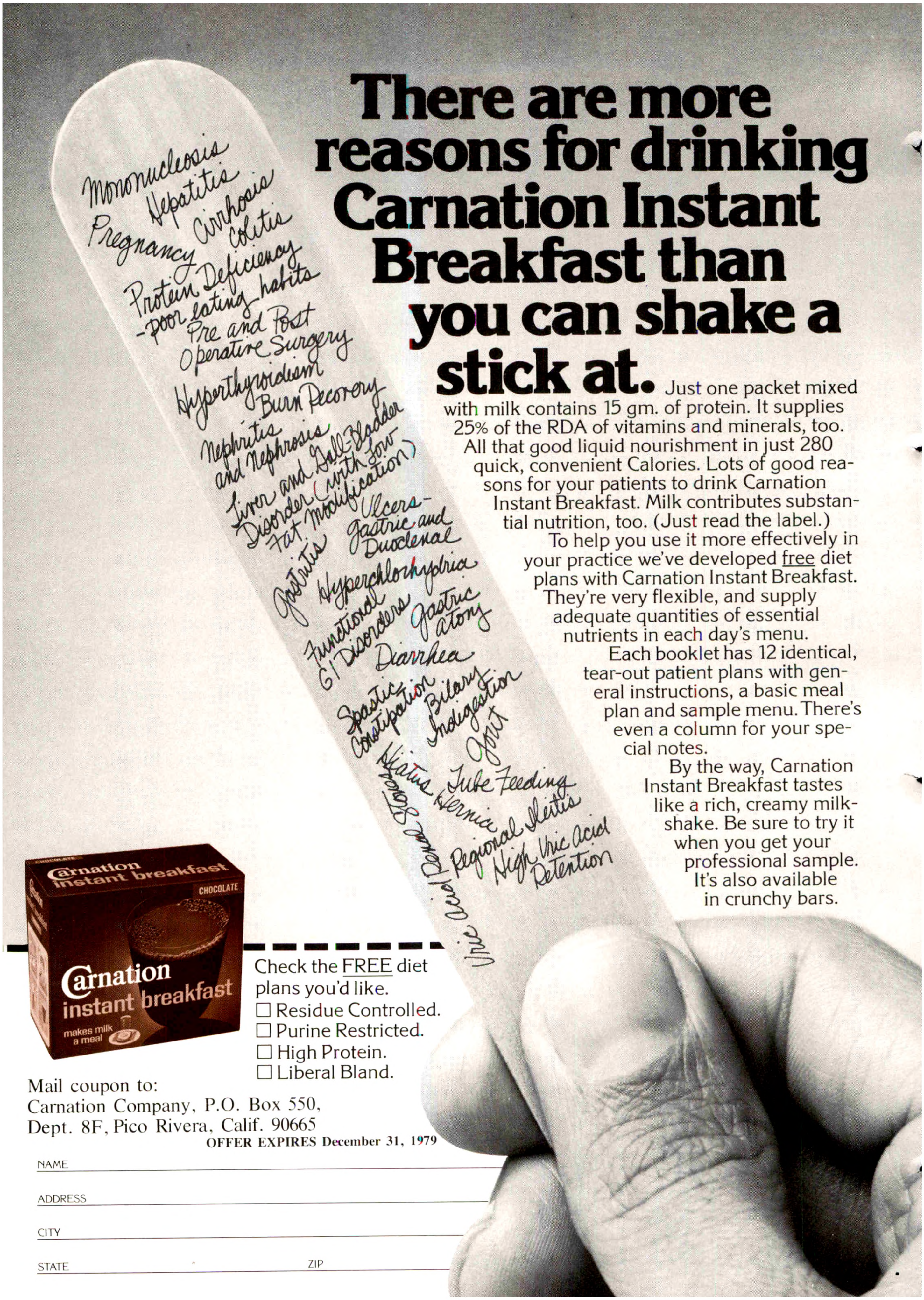
There are more reasons for drinking Carnation Instant Breakfast than you can shake a stick at.

Just one packet mixed with milk contains 15 gm. of protein. It supplies 25% of the RDA of vitamins and minerals, too. All that good liquid nourishment in just 280 quick, convenient Calories. Lots of good reasons for your patients to drink Carnation Instant Breakfast. Milk contributes substantial nutrition, too. (Just read the label.)

To help you use it more effectively in your practice we've developed free diet plans with Carnation Instant Breakfast. They're very flexible, and supply adequate quantities of essential nutrients in each day's menu.

Each booklet has 12 identical, tear-out patient plans with general instructions, a basic meal plan and sample menu. There's even a column for your special notes.

By the way, Carnation Instant Breakfast tastes like a rich, creamy milkshake. Be sure to try it when you get your professional sample. It's also available in crunchy bars.



Check the FREE diet plans you'd like.

- ☐ Residue Controlled.
- ☐ Purine Restricted.
- ☐ High Protein.
- ☐ Liberal Bland.

Mail coupon to:
Carnation Company, P.O. Box 550,
Dept. 8F, Pico Rivera, Calif. 90665

OFFER EXPIRES December 31, 1979

NAME ______

ADDRESS ______

CITY ______

STATE ______ ZIP ______

If slippage has you down...

we'll keep you up.

T.E.D.®

Full Leg Anti-Embolism Stockings

- Side panel and waist belt assure reliable continuous non-slip protection
- Graduated compression from ankle to upper thigh — insures optimum blood flow
- Seamless construction to eliminate harsh ridges
- Pressure break protects critical popliteal area and insures free movement
- Contoured instep provides flexibility for patient exercise
- Inspection toe opening provides easy access for medical examination

KENDALL
INNOVATORS IN PATIENT CARE

Contraindications: Stockings may not be recommended for patients with the following: **1.** Any local leg condition in which stockings would interfere, such as: **a.** dermatitis, **b.** vein ligation (immediate post-operative), **c.** gangrene, **d.** recent skin graft. **2.** Severe arteriosclerosis or other ischemic vascular disease. **3.** Massive edema of legs or pulmonary edema from congestive heart failure. **4.** Extreme deformity of leg. **5.** For thigh length, patients with a circumference greater than 25 in. (63.5cm) at the gluteal furrow. For full-leg (X-S,S,M,L), patients with a circumference of 25 in. (63.5cm) or greater at the gluteal furrow. For full-leg (X-L), patients with a circumference greater than 32 inches (81.3cm) at the gluteal furrow.
Precautions: 1. Proper sizing and application must be assured. **2.** For full-leg style T.E.D. Stockings avoid interference of side panels or waistband with incisions, drainage tubes, catheters or other exterior devices.
Warnings: Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

© 1978, The Kendall Company ■ Hospital Products ■ One Federal Street ■ Boston, MA 02101

Announcing…
a significant advance
in oral cephalosporin
therapy

Lick Observatory photograph

New B.I.D. dosage velosef®

CEPHRADINE, SQUIBB

Clinically and bacteriologically comparable to Q.I.D. dosage*

		Excellent/Good
in *urinary tract infections***	Capsules **B.I.D.**	90% (253 patients)
	Capsules **Q.I.D.**	89% (262 patients)
in *upper respiratory tract infections, including otitis media***	Capsules **B.I.D.**	99% (158 patients)
	Capsules **Q.I.D.**	98% (149 patients)
in *lower respiratory tract infections***	Capsules **B.I.D.**	92% (82 patients)
	Capsules **Q.I.D.**	98% (79 patients)
in *skin and soft tissue infections***	Capsules **B.I.D.**	94% (70 patients)
	Capsules **Q.I.D.**	95% (59 patients)

Advantages of twice-daily (q12h) oral dosage

More convenient for ambulatory and non-compliant patients to take medication

Eliminates "round-the-clock" scheduling—patients don't have to be awakened for their medication

Can be taken with a meal—around breakfast and dinner time for heightened compliance

*Data on file at Squibb Institute for Medical Research

**See brief summary on following page for susceptible organisms and recommended dosage

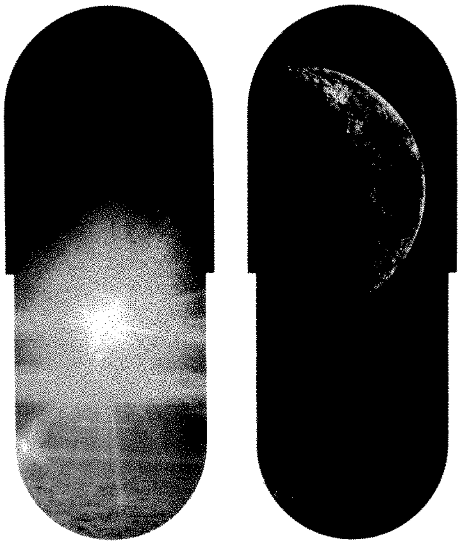
velosef®

CEPHRADINE, SQUIBB

Capsules and Powder for Oral Suspension

B.I.D. or Q.I.D.... now you have a choice

Please see following page for brief summary.



velosef®

CEPHRADINE, SQUIBB

Capsules and
Powder for Oral Suspension
B.I.D. or Q.I.D.
...now you have a choice

VELOSEF® CAPSULES
Cephradine Capsules

VELOSEF® for ORAL SUSPENSION
Cephradine for Oral Suspension

DESCRIPTION: Velosef '250' Capsules and Velosef '500' Capsules (Cephradine Capsules) provide 250 mg. and 500 mg. cephradine, respectively, per capsule. Velosef '125' for Oral Suspension and Velosef '250' for Oral Suspension (Cephradine for Oral Suspension) after preparation provide 125 mg. and 250 mg. cephradine, respectively, per 5 ml. teaspoonful.

INDICATIONS: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever: Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Soft Tissue Infections due to staphylococci; Urinary Tract Infections, including prostatitis, due to *E. coli*, *P. mirabilis* and *Klebsiella* sp.

Note: Culture and susceptibility tests should be initiated prior to and during cephradine therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin C derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).*

In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Usage in Pregnancy and Lactation: Although no teratogenic or anti-fertility effects were seen in reproduction studies in mice and rats receiving up to four times the maximum human dose, the safety for use in human pregnancy has not been established; weigh benefits in pregnant women against possible risk to the fetus. Cephradine is secreted in breast milk during lactation.

PRECAUTIONS: To detect any side effects or unusual manifestations of drug idiosyncrasy, follow patients carefully. Discontinue drug and treat with the usual agents (e.g., pressor amines, antihistamines or corticosteroids) if a hypersensitivity reaction occurs.

Administer cephradine with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during cephradine therapy since cephradine accumulates in the serum and tissues. Patients with impaired renal function require a modified dosage schedule (see package insert).

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy.

After treatment with cephradine, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®.

Recognize that a post-treatment positive Coombs test may be due to the drug since a false positive direct Coombs test has been reported after treatment with other cephalosporins.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I.—glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain, heartburn. Skin and Hypersensitivity Reactions—mild urticaria or skin rash, pruritus, joint pains. Blood—mild transient eosinophilia, leukopenia and neutropenia. Liver—transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal—Transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others—dizziness, tightness in chest, and candidal vaginitis.

DOSAGE: Adults—For respiratory tract infections (other than lobar pneumonia) and skin and soft tissue infections: 250 mg. q. 6 h. or 500 mg. q. 12 h. For lobar pneumonia and urinary tract infections: 500 mg. q. 6 h. or 1 g. q. 12 h. Severe or chronic infections may require larger doses.

Children over 9 months of age—25 to 50 mg./kg./day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg./kg./day in equally divided doses q. 6 or 12 h. but not to exceed 4 g./day. Dosage for children should not exceed dosage recommended for adults. There is no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

For full prescribing information, consult package insert.

HOW SUPPLIED: 250 mg. and 500 mg. capsules in bottles of 24 and 100 and Unimatic® single-dose packs of 100. 125 mg. and 250 mg. for oral suspension in bottles of 100 ml.

©1977 E. R. Squibb & Sons, Inc. 787-509

SQUIBB® "The Priceless Ingredient of every product is the honor and integrity of its maker."™

Viokase® costs your patients less than other pancreatic preparations

4x N.F. Protease
6x N.F. Amylase
10 x N.F. Lipase
(whole pancreas)

Twenty-Five Year Veteran

NDC 668-0013-01
Viokase®
Description: VIOKASE is a pancreatic enzyme concentrate of porcine origin containing standardized lipase, protease and amylase activities plus esterases, peptidases, nucleases and elastase.
CAUTION: Federal Law Prohibits Dispensing Without Prescription
100 TABLETS
325 mg EACH
VIOBIN

in the management of exocrine pancreatic deficiencies

The effectiveness of Viokase is confirmed by over twenty-five years of clinical experience . . . and it still costs your patients less than other pancreatic preparations. Current literature[1,2] documents the use of Viokase as a digestive aid in cystic fibrosis and in exocrine pancreatic deficiencies usually due to chronic pancreatitis, pancreatectomy or obstruction in the pancreas caused by malignant growth.

1. Kafka, E. and Klaser, H.: "Pancreatic Disease", *Postgraduate Medicine*, 57: 140-145, 1975.
2. Long, W.B. and Weiss, J.B.: *Gastroenterology*, 67:920-925, 1974.

VIOKASE®
(pancreatin)

Description: VIOKASE is a pancreatic enzyme concentrate of porcine origin containing standardized amylase, protease and lipase activities plus esterases, peptidases, nucleases and elastase.

The enzyme potency of the tablets and powder are:

	Each 325 mg. Tablet	Each 0.75 gram (⅓ teaspoonful)
Lipase, N.F. Units	6.500	15.000
Protease, N.F. Units	32.000	75.000
Amylase, N.F. Units	48.000	112.500

Under conditions of the N.F. test method (in vitro) VIOKASE has the following total digestive capacity:

	Each 325 mg. Tablet	Each 0.75 g. Powder
Dietary Fat	23	53 grams
Dietary Protein	32	75 grams
Dietary Starch	48	112 grams

VIOKASE Tablets are not enteric coated.

Indications: As a digestive aid in cystic fibrosis and in exocrine pancreatic deficiencies usually due to chronic pancreatitis, pancreatectomy or obstruction in the pancreas caused by malignant growth.

Administration and Dosage:
Powder: Dosage to patients with cystic fibrosis: ⅓ teaspoon (0.75 grams) with meals.
Tablets: Dosage to patients with cystic fibrosis or chronic pancreatitis —1 to 3 tablets with meals. For aiding digestion in patients with pancreatectomy or gastrectomy—1 to 2 tablets taken at 2-hour intervals, or as directed by physician.

Caution: Federal law prohibits dispensing without prescription.

Warnings: Avoid inhalation of powder.

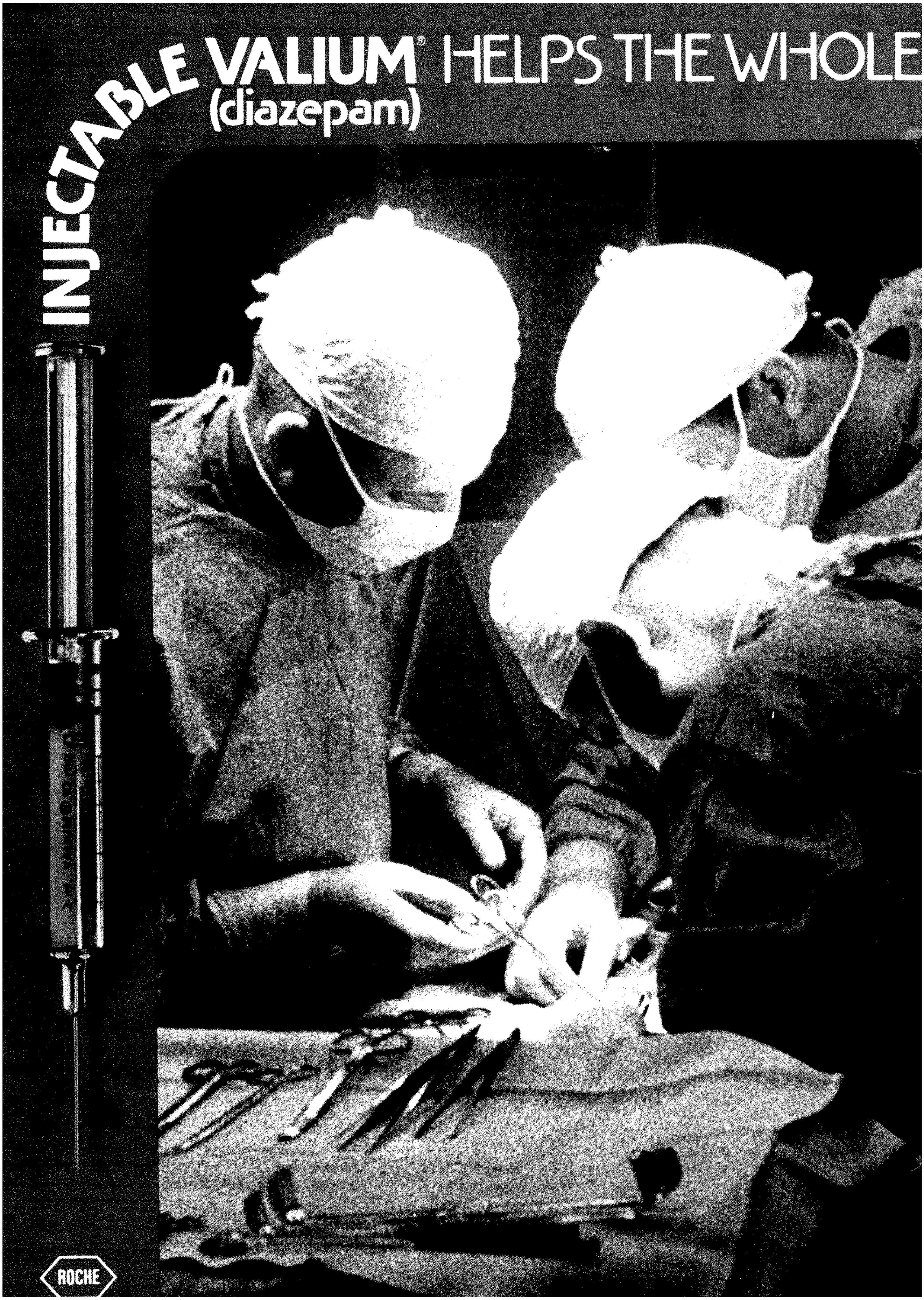
Precautions: Use with caution in patients known to be allergic to pork protein.

How Supplied:
Powder: Bottles of 4 ounces and 8 ounces
Tablets: Bottles of 100 and 500

Literature Available: Complete literature available upon request including information on BEEF VIOKASE DERIVED FROM BEEF PANCREAS FOR THOSE EXCEPTIONAL PATIENTS ALLERGIC TO PORK.

VIOBIN

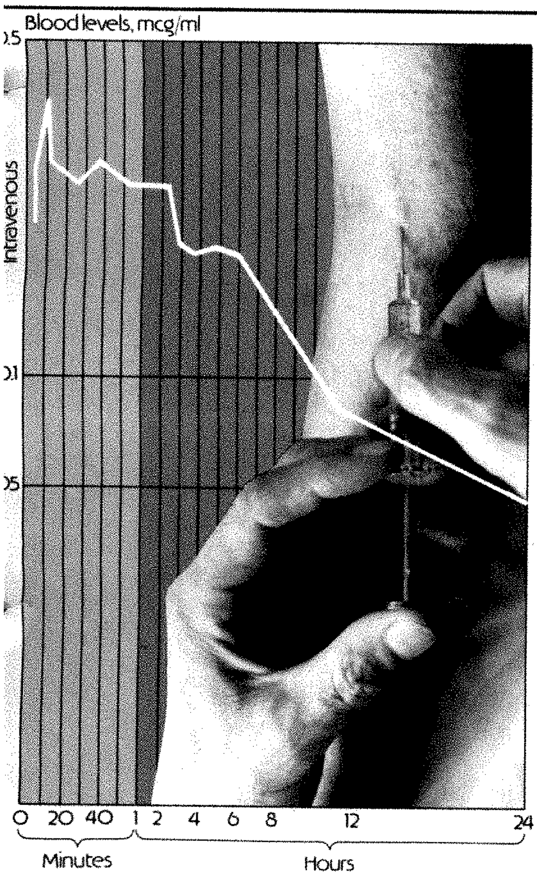
VIOBIN CORPORATION
A Subsidiary of A.H. Robins Company
Monticello, IL 61856


INJECTABLE VALIUM® HELPS THE WHOLE
(diazepam)
ROCHE

PROCEDURE GO MORE SMOOTHLY

MAY BE GIVEN I.V. FOR RAPID ONSET OF ACTION

EASILY TITRATED TO DESIRED RESPONSE



Adapted from Kaplan SA, *et al.* *J Pharm Sci* 62: 1789-1796, Nov 1973

I.V. administration makes it possible to titrate the dosage of Injectable Valium to the desired degree of response. This is particularly important when prompt calming, muscle relaxant or anticonvulsive action is required, and when the patient's reaction to medication must be monitored closely.

DIMINISHED RECALL WHEN GIVEN I.V.

As preoperative medication, I.M. administration of Injectable Valium is the preferred route. When administered intravenously, Injectable Valium usually produces anterograde amnesia of rapid onset and short duration. When given intravenously prior to surgery, for example, most patients cannot recall the induction period.

Injectable Valium® (diazepam) Ⓒⅳ

A broad range of benefits in one effective agent

Please see last page of this advertisement for a summary of product information

Injectable Valium® (diazepam)

A broad range of benefits in one effective agent

Can be administered I.M. or I.V.

Rapid onset of action

Easily titrated I.V.

Please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs, or add to I.V. fluids.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms (similar to those with barbiturates, alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal/muscle cramps, vomiting, sweating). Keep addiction-prone individuals under careful surveillance because of predisposition to habituation/dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus; severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Reassessment of Intraoperative Decisions:

Why Operations for Cancer of the Large Bowel Fail

CARL O. KNUTSON, M.D., DONALD E. FRY, M.D., RONALD D. BARBIE, M.D., HIRAM C. POLK, M.D.

From the Department of Surgery,
University of Louisville School of Medicine,
Health Sciences Center, Louisville, Kentucky

A program developed for the intraoperative judgment decisions commonly faced in cancer of the colon and rectum has been published and has been found to correlate frequently with the management carried out in a cancer hospital and on the ward services of university programs in city/county and Veterans Administration hospitals. Those patients whose management varies with the recommendations of the program are subject to statistically significant excess risk of dying in the hospital and excess risk of failure of ultimate control of their malignant process. It is our opinion that this program is not only useful in demonstrating the explicit nature of surgical judgment but is also useful to the operating surgeon as an indication for the need for consultation or reassessment of his observations.

FEW MORE PERSISTENT PROBLEMS exist than the control of cancer of the large bowel. It perenially ranks among the two most frequent killers among neoplastic diseases in the adult North American population and is the source of substantial morbidity. Indeed, there are few other problems that are at once so familiar and yet so persistently vexing. Periodically one will note proposals advocated as major advances in the control of such neoplasms. More often than not, however, when subjected to further scrutiny, comparison and analysis, these proposals have been disappointing. By reviewing trends and results in the management of cancer of the colon and rectum over several decades rather than shorter periods of time, one can better perceive the truly significant patterns. As a result of such studies, Ederer[2] and others[6,7] pointed out that the only real progress made in the management of cancer of the colon and rectum in the first half of this century was due to: 1) a substantial increase in the operability and resectability, and 2) a very sharp decrease in the risk of treatment, *i.e.*, death in the hospital after operation.

Reports concerning special operative technics and adjunctive systemic or local chemotherapy or radiotherapy have been enthusiastically received. Each of these modalities have produced equivocal improvement and represent observations of which the majority have not been confirmed by further investigation. Most assuredly, an approach to cancer of the colon and rectum which would truly increase patient survival and decrease morbidity, both from the illness and from treatment thereof, is a genuine need.

As part of a continuing analysis of cancer of the colon and rectum and the associated results of diagnostic and therapeutic manuevers, a special programmatic approach was envisioned and developed.[4] This approach (CAMEO) emphasized 1) identification of those characteristics of patients which would facilitate favorable definitive surgical therapy, and 2) meticulous definition of the nature of the operative procedure. The former project, obviously a more complicated proposition, is in the process of development and refinement. The latter process, which was developed as a potential aid to intraoperative management of colorectal carcinoma, defines operative judgment, intraoperative therapeutic decisions and other technical considerations. By utilizing a computer management protocol in this endeavor, the surgeon is provided appropriate treatment alternatives based on objective input of observations at the time of operation. The data input consists of 1) the anatomic location of the primary lesion, 2) the presence or absence of distant metastases, 3) the involvement of contiguous structures by the pri-

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests: Carl O. Knutson, M.D., Department of Surgery, University of Louisville School of Medicine, Health Sciences Center, Louisville, Kentucky 40202.

Supported in part by the Kentucky Division, American Cancer Society, and American Cancer Society Fellowships 3849 (Dr. Fry) and 3850 (Dr. Barbie).

Submitted for publication: December 8, 1977.

0003-4932-78-0500-0549-0075 © J. B. Lippincott Company

TABLE 1. *Consecutive Operated Cases Analyzed*

Private community hospital	(A)	171
City-County teaching hospital	(B)	97
Veterans administration hospital	(C)	93
		361

mary lesion, and 4) the presence or absence of perforation or obstruction. From these observations, treatment alternatives based on the most currently accepted surgical information are provided by the computer logic scheme. Factors applicable to treatment alternatives are the extent of colonic resection, advisability of primary anastomosis, and other adjunctive measures (*i.e.*, drains and/or delayed primary closure of the incision itself).

Utilizing the investigational and clinical skills of individuals with a particular interest in cancer of the colon, the scheme was tested against actual practices in a hospital with a patient base representing predominantly referred problems in neoplastic disease. A 96% correlation was identified. This emphasized the program's usefulness as an explicit example of proper intraoperative surgical judgment: perhaps as a guideline for peer review process for young surgeons and possibly as a "pilot's checklist" for more experienced surgeons.

Ravitch[8] and others[3] have formally and informally criticized both the concept and the system, emphasizing primarily that judgments involved in the program were simple and within the capability of virtually all certified, practicing surgeons. Furthermore, the problem of obtaining appropriately accurate descriptions of operative findings for input and cumbersome technology represented other criticisms. Ravitch also questioned whether the initial high correlation was related to overlapping responsibilities and identities between the program developers and the operating surgeons at the hospital in question. He furthermore suggested testing of the program in an unrelated clinical setting.

Method

To examine the system in light of these thoughtful critiques, we then set out to compare the intraoperative management of patients with carcinoma of the colon and rectum within our university affiliated system and to determine the applicability of the principles and of the concept. Accordingly, we examined the operative records in 361 consecutive operations performed in university affiliated hospitals of somewhat different characteristics. The cases studied were characterized by: 1) the presence of only one primary colorectal cancer; 2) the ability to tolerate any appropriate surgical procedure; 3) the surgeon being capable of performing any appropriate operative procedure.

The institutions which have been further defined in prior publications[1,6] regarding overall care of carcinoma of the colon, may be characterized as follows: Hospital A is a private hospital with a formal affiliation with the Department of Surgery at the university. Its entire surgical staff are Fellows of the American College of Surgeons and 90% of that staff have been certified by the American Board of Surgery. In every case, the individual operating surgeon was solely responsible for intraoperative decisions; no protocol of any sort was under study or in effect at the time. Hospital B is a city/county 350 bed hospital with a population that represents primarily the medically indigent of the city and county, plus some complicated, referred "teaching" cases. Hospital C is a 450 bed Veterans Administration Hospital affiliated through a Dean's Committee with the University of Louisville. Its patient population is representative of such regional institutions and therefore may be commonly recognized as predominantly male with a past history of military service. Operations performed at Hospitals B and C were performed by residents directed and usually assisted by University surgical faculty. Because of the retrospective nature of the study, the operative decisions in Hospitals B and C were not determined by protocol or the CAMEO concept.

The 361 cases from the three hospitals were reviewed: 171 cases from Hospital A, 97 cases from Hospital B and 93 cases from Hospital C (Table 1). The cases were analyzed in view of preoperative and operative findings and were tabulated according to the CAMEO protocol. The operative judgments and treatment options carried out were correlated with the expected choice(s) determined by the computerized logic flow diagrams. If two or more treatment alternatives were listed in the logic flow diagram, the case was considered correlated if the operation performed matched with *any* of the choices.

Data from correlating and noncorrelating cases were then analyzed for postoperative morbidity, operative (hospital) mortality, and long-term patient survival. Chi square statistical analysis was utilized to evaluate differences between correlating and noncorrelating groups. Probability values of less than 0.05 were considered statistically significant and analysis of the power of the test having values greater than 90% were considered reproducible.

The flexibility of the program may be best exemplified by a hypothetical patient with a curable obstructing carcinoma of the sigmoid colon. Program suggested management for that patient is: 1) diverting colostomy with subsequent resection, anastomosis, and later

TABLE 2. *Comparison of Postoperative Morbidity, Mortality and Survival Between Cases in Which CAMEO Could and Could Not Evaluate*

	Total	Postoperative Morbidity	Operative Mortality	Survival 5 years	P	PT
Postoperative Morbidity						
CAMEO could evaluate (++;+0)	347	84 (24%)				
CAMEO could not evaluate (00)	14	7 (50%)			.06*	.70†
Operative (Hospital) Mortality						
CAMEO could evaluate	347		31 (9%)			
CAMEO could not evaluate	14		6 (43%)		.0006	.90
Long-term Survival (5 years or more)						
CAMEO could evaluate	347			134 (39%)		
CAMEO could not evaluate	14			0	.008	.95

* Probability.
† Power of the test.

colostomy closure, or 2) resection with proximal colostomy and either exterization of the distal colon through a mucous fistula or closure as a Hartmann pouch, or 3) resection and anastomosis with a proximal diverting colostomy.

Results

Three major categories in terms of correlation were identified. The first is that there was correlation between what was actually done and what was program-recommended (++), the surgeon in question following in general the recommendations reflected in the program. The second category is a group of patients whose intraoperative findings were so complex as to not be suitable for analysis within the constraints of the existing program (00). The third category represents those patients in which the intraoperative management deviated from the program-recommended care (+0). The basic results of this comparison are displayed in Tables 2–6. These tables may be summarized narratively as follows: those patients in whom operative findings were so complex as to not be suitable for comparison with the programmatic recommendations obviously represented extraordinarily unusual and perplexing situations and, not surprisingly, this particular combination of events eventuated in a 43% hospital mortality rate, a postoperative complication rate of 50%, and no patient was cured of his colorectal cancer (Table 2). Those patients whose treatment correlated precisely with the program-recommended operative procedures, whether examined within each institution or the groups as a whole, bore the lowest treatment mortality rate, the lowest complication rate and the highest five-year survival rate of any of the subgroups eligible for analysis (Table 3). To the contrary, those patients whose operative management deviated from the protocol were associated with statistically significant increases in hospital mortality rates and decreases in five year survival. The increase in complication rate noted in these patients was impressive but did not reach a level of statistical significance.

The most common deviations from the protocol by the operating surgeon or surgeons were two-fold (Table 4). The tendency to treat partial or complete colonic obstruction with less than optimum respect resulted in compromise: the avoidance of colostomy and diversion in favor of primary anastomosis even though partial or complete colonic obstruction was *recognized* (Table 5). The second major area of disagreement was associated

TABLE 3. *Three Hundred Forty-seven Cases CAMEO Program Could Evaluate: Correlation Between Actual and Program-suggested Operative Treatments*

	Treatments correlated	Total	Postoperative Morbidity	Operative Mortality	Survival 5 or more years	P	PT
Postoperative Morbidity	Yes (++)	307	70 (23%)			0.13*	0.50†
	No (+0)		14 (35%)				
Operative (Hospital) Mortality	Yes (++)	307		23 (7%)		0.02	0.85
	No (+0)			8 (20%)			
Long-term Survival (5 years or more)	Yes (++)	307			126 (41%)	0.02	0.85
	No (+0)	40			8 (20%)		

* Probability.
† Power of the test.

TABLE 4. *Cases Deviating from CAMEO (+0) in 40 Patients*

Reasons for Deviation from CAMEO			
Anastomosis associated with partial/complete obstruction	21/40	(53%)	73%
Palliative rather than curative procedure	8/40	(20%)	
Significantly more colon removed than required	1/40	(2%)	
Other reasons (includes tumor transection)	10/40	(25%)	

with failure to adequately excise a clinically curable colon cancer—the tendency being to leave possible tumor extension on adjacent organs or sites rather than expand the scope of the operation (Table 5). Thus one sees the peculiar paradox of a relatively radical (*i.e.* aggressive) surgical approach for obstructing lesions and an overly conservative approach with respect to those occasional colon cancers which show some signs of local extension but no real signs of incurability.[5] The former error contributes to increased hospital morbidity and mortality and the latter reduces opportunity for long-term cure.

One may readily see that digressions from the recommended intraoperative management occurred significantly more commonly in the private affiliated hospital than in the city/county and Veterans Hospital (Table 6). One patient in six undergoing operative management of a cancer of the colon or rectum in Hospital A was subjected to an operative procedure at significant variance with that which was program-recommended.

Discussion

In respect to the medical welfare of the North American population, few lesions by virtue of prevalence, morbidity, or intrinsic death rate are more worthy of attention and improvement than adenocarcinoma of the colon and rectum. We must continue to evaluate all adjunctive modalities, in addition to each new technical innovation, with care and precision. However, reconsideration of the basic principles of colon surgery enable us to determine how often significant deviations from the time-honored and *proven* treatment modalities occur. Thus the study in questions indicates that there is both need and opportunity for improvement. Perhaps as many as 15% of operations, even when performed by Board certified surgeons who are also Fellows of the American College of Surgeons, represent significant digression from what is deemed optimum treatment under the circumstance. The clinical significance of these deviations is profound. The observations closely correlate with the short and long-term results which are the appropriate parameters for the assessment of any chronic illness. Furthermore, there is direct correlation between overly aggressive management of the obstructed colon and postoperative morbidity and mortality. On the other hand, inadequately aggressive management of the biologically favorable tumor which is locally extensive increases the probability of an uncomplicated postoperative recovery but significantly decreases the change for long-term cure. These observations vary with those principles expounded in the course of surgical meetings or through other contacts with certified surgeons. In such relaxed settings, one rarely encounters a surgeon who is not very conservative about the management of the totally or partially obstructed colon. It seems that surgeons don't always practice the principles they recognize. On the contrary, one does on occasion note surgeons who have not appreciated the unusually favorable characteristics of some extensive colorectal carcinomas. As a result of analysis of these records, we propose that during the course of the operation some surgeons subconsciously de-emphasize the significance of colonic obstruction and local extension of a curable tumor and find themselves justifying an operative procedure hopefully aimed at a live, happy patient with no colostomy. The data indicate that this practice is an expensive compromise.

TABLE 5. *Hospital Morbidity Among Cases Deviating From CAMEO (+0)*

	Postoperative (Hospital) Morbidity			
	No Morbidity (26)		Morbidity (14)	
Reason for Deviation	No. of Patients	%	No. of Patients	%
Anastomosis associated with partial/complete bowel obstruction	10	38%	11	79%
Palliative rather than curative procedure	8	31%	0	
Significantly more colon removed than required	1	4%	0	
Other reasons (includes tumor, transection)	7	27%	3	21%
	26		14	

TABLE 6. *Correlation with CAMEO in Three Differing Hospital Settings*

		Correlated	
Hospital	Total	Yes	No
A	166	83%	17%
B	90	93%	7%
C	91	95%	5%
	347	88%	12%

It seems that this analysis has, to the extent possible in a retrospective study, refuted some of the criticisms of the CAMEO concept. In the course of an operation for colon or rectal cancer, a portion of certified surgeons will make inappropriate decisions that would not be justifiable before their peers nor probably in the light of their own analysis at some other less pressured time and place.

The ability of the CAMEO program to deal with the operative findings in some 96% of these cases is evidence of its applicability and further suggests that the program might be very useful as an analogy to the "pilot's checklist." One could simply enter the operative observations into the program, thereby making certain that the treatment about to be provided was consistent with the best analysis resulting from the program. We feel that a noncorrelating response would be an indication for intraoperative consultation with another surgeon, suggesting either that the case exceeds the program's present stage of development, and therefore is not suitable for comparison, or that the operating surgeon has made an error in his observations or judgments.

This program, we feel, is not only useful in demonstrating the explicit nature of surgical judgment but is also useful to the operating surgeon as an indication for the need for consultation or reassessment of his observations.

Further real advances in the management of the patient with cancer of the colon and rectum are going to be hard fought and hard won. It appears that this is an area in which some patients could have their care improved tomorrow.

Acknowledgment

The authors wish to acknowledge the assistance of Donna White, M.D. in the initial stages of this work.

References

1. Baughman, B. B., Ahmad, W., Knutson, C. O. and Polk, H. C., Jr.: The Surgical Treatment of Carcinoma of the Colon and Rectum: An Index of Quality Care and its Sociologic and Geographic Distribution. Ann. Surg., 183:550, 1976.
2. Ederer, F., Cutler, S. J. and Eisenberg, H., Jr.: Survival of patients with Cancer of Large Intestine and Rectum: Connecticut 1935–1954. J. Natl. Cancer. Inst., 26:489, 1961.
3. Fielding, P. and Dudley, H.: Letter: Computer Logic Programs. Surgery, 77:730, 1975.
4. Knutson, C. O. and Watson, F. R.: Preliminary Results of a Computer Logic Program for the Operative Management of Colon Cancer. Surgery, 76:298, 1974.
5. Polk, H. C., Jr.: Extended Resection for Selected Adenocarcinoma of the Large Bowel. Ann. Surg., 175:892, 1972.
6. Polk, H. C., Jr., Ahmad, W. and Knutson, C. O.: Carcinoma of the Colon and Rectum. Curr. Prob. Surg., Chicago, Year Book Med. Publ., pp. 1–64, January, 1973.
7. Polk, H. C., Jr., Spratt, J. S., Jr., Bennett, D., et al.: Surgical Mortality and Survival from Colonic Carcinoma. Arch. Surg., 89:16, 1964.
8. Ravitch, M. M.: Editorial: Computer Logic in the Operating Room. Surgery, 76:202, 1974.

DISCUSSION

DR. BRANHAM B. BAUGHMAN (Frankfort, Kentucky): When Dr. Polk asked me to discuss this paper, I was reluctant, because I don't like to discuss my unsuccessful cases, and about all I can add to this is some of the things which I did years ago which Dr. Polk says not to do now.

As most of you know, since 1905, when William Ernest Miles did his work on cancer of the rectum, we have had 70 years in which, as Dr. Polk said, we have not improved too much in the five and ten year survival, except for certain unusual and excessively fine reports by men like Dr. Turnbull and our own Drs. Beahrs and McSwain and others who have reported good results.

Now, Mr. Miles was a very courageous man. In 1908, when he reported his first series of cases, his hospital mortality was 44%. That would certainly discourage me, and, I think, a good many of us. But he had what Dr. Byrd said the other day—patience, with a "c-e", and persistence—and we have made some improvements, shown by many of these men.

Despite all these good reports, a year ago the National Institutes of Health reported that overall in the United States the survival for cancer of the colon and rectum was between 45 and 50%, which is still not good. It's the second killer of cancer, as you know, second to lung cancer.

Now, a good many of you here, I see, were in what I like to call "our war," World War II, in the military service, as I was, in the Army, and prior to World War II there was one gentleman who had written and spoken and done, probably, more about cancer of the colon than anybody else. He was a former member and President of this society, Dr. Fred Rankin. During the war he became the surgical consultant to the Surgeon General of the Army. He became General Rankin, and prior to the war he devised a very unique, safe operation, before antibiotics and intestinal antiseptics. He called it obstructive resection. He devised a very unique three-bladed clamp. It was actually a modification of the old Block-Paul-Mikulicz exteriorization, but it was safe. It was an improvement.

So I had the occasion in the Army hospital where I was situated to see two patients under the age of 30 within about a year of each other with intestinal obstruction, proven to be tumor of the left colon. Now, I guess every Army hospital then had a Rankin clamp, and I was not about to do anything else, for two reasons. First, it was a good, safe operation. Secondly, when General Rankin came around to inspect us, if I had done anything else, in about 24 hours I would have had orders to China, Burma, or as far away as the Army could send me, because General Rankin didn't brook much disagreement, as Coleman Johnston well knows, and Mel Bernhard, and others who knew him.

So I did his operation on these two soldiers. Of course, you could not resect a very wide mesentery, one of the things that Dr. Polk and his colleagues talk about. But I did these boys, and finally closed their colostomies. They were discharged from the hospital, given CDD's from the Army, and their pockets were full of self-addressed cards to me.

One of them I never heard from. The other one I did hear over a period of about a year and a half, and, unfortunately, he died in Veterans Hospital of metastasis, which was not totally unexpected. But I did what I thought then was a safe operation, although it's not done today. We think we have improved a good deal.

Now, I have three other cases which are also not all successful. (Slide) This is an old gentleman who came in with obstruction of the colon. I did what is, I think, the accepted procedure on him. I did a transverse colostomy.

(Slide) Then I did a resection, and later closed the colostomy, and got him out of the hospital. It was a long, tiresome procedure, and after about a year he died of metastasis.

Now, I have had a few others in which I did preliminary colostomy, and I have not been very successful. That's just because I'm not a very good surgeon. But anyway, I think I did what Dr. Polk says: Don't do a primary resection in the face of obstruction. I followed his advice there.

Now the next one is (slide) a woman who had no obstruction, but she had a very definite tumor low in the sigmoid. She had fever. She was quite sick. And that was almost 30 years ago, and I had more courage than sense, and I did a primary resection on her. She had a perforation. I put a drain in. She recovered. She lived to the age of 85—died just a few years ago—and she was cured.

I don't think what I did was very wise.

(Slide) This is a younger woman, 43. This was 20 years ago. She had this lesion which you can see in her left colon.

(Slide) I did what I thought was a pretty good resection on her; but you see the node right there. (Indicating) That was the only node in the mesentery that had metastasis; and I thought I had cured this girl. She recovered without any trouble from the operation. Unfortunately, a year and a half later she died of cerebral metastases.

So, undoubtedly, I did not resect enought mesentery; as Dr. Polk says, if you're going to do a curative operation do a good one, take enough, and try to cure them. These are just some things that maybe you should, and maybe you shouldn't do.

Dr. Roger S. Wotkyns (Wheat Ridge, Colorado): Dr. Polk has dramatically reinforced the notion that good judgment and the application of proven technique results in success. Here he has applied a method, the sequential, branching logic statement, sometimes called an algorithm, or decision tree, in the intraoperative management of colonic cancer, in ordering one's thought and judgment through the course of an operation for cancer of the colon. The result is obvious. The message is stated admirably. One might argue the details of a logic statement, but not the method.

Dr. Ben Eiseman, one of your members, and I recently completed a book called *Surgical Decisions* to be published in May of next year, in which 140 such decision trees are presented. (Slide) For comparison's sake, here is a preliminary algorithm which we compiled for colon cancer. One might argue that this simplistic logic statement is a crutch, rather than a vehicle, in the learning process. We submit that considerable knowledge is necessary in the understanding of the algorithm, obviously, and it's more accurate to say that this is a guide to the orderly application of knowledge.

(Slide) The next slide is another example, that of pelvic fracture, another difficult preoperative and intraoperative management problem that yields to a logic statement. Here the problems associated with pelvic fracture are stated, and the organization and the orderly, sequential steps may be of value in the preoperative approach to the problem.

Dr. Isidore Cohn, Jr. (New Orleans, Louisiana): As Dr. Polk has indicated, the stimulus for this particular paper was a comment by another member about some problems with the original presentation of a computer logic system for decision-making in the operating room. Some of the earlier criticisms have been answered, but some other problems are still in need of answers.

As one listens to Dr. Polk, or as one reads his manuscript, it becomes obvious that there are a number of places where the surgeon has made the wrong decision, even though he has seen the right information. If the surgeon in the operating room is punching the wrong information into his subconscious computer, then it is probably true that he would punch the wrong information into the mechanical computer, no matter how good the computer is.

If he punched the wrong information in, then he is going to get the wrong information out. Or if he gets the right information out, and has subconsciously made up his mind in another direction, he will not pay attention to the information that comes from the computer. I don't think we have resolved that part of the problem, which is why Dr. Polk has indicated a number of inappropriate operations have been done.

I wonder how he proposes to get a particular surgeon to answer the right thing as he proceeds in the operating room.

There's one other interesting problem that he has discussed. The bulk of the erroneous decisions were made in Hospital A, which is a private hospital where the vast bulk of the surgeons are Board certified and members of the College. Most of the right decisions were made where there were residents in training, or under very careful staff supervision.

Since the men in the private hospital are doing things they shouldn't be doing, and since they represent the bulk of surgery in this country, how are we going to get them to listen to the computer more frequently?

Dr. Richard G. Martin (Houston, Texas): I rise only to emphasize that I think this is a very important paper at this time, especially with the philosophy that seems to be generating that we can do lesser procedures, and cover it with chemotherapy and x-ray therapy, or adjuvant therapy of some kind. I do not believe this is possible with colon cancer. I think we must go through such a procedure as Dr. Polk has outlined, and carry out these procedures, and then think of chemotherapy afterwards, and not to cover our mistakes.

Dr. Carl O. Knutson (Closing discussion): In reference to Dr. Baughman's remarks: Obviously, in ten minutes we cannot describe the details of the entire program. The objective of this phase of CAMEO is to present the surgeon with most acceptable alternatives given specific variables observed at the operating table. Therefore, relative to the cases presented by Dr. Baughman, the therapeutic options selected were not the only acceptable options offered by the computer program and, possibly, one of the other alternatives might have been more suitable under the existing clinical circumstances. One would have to study all of the algorithms to fully realize that this program is not restrictive within the framework of good surgical judgement and the application of sound basic surgical principles.

I sincerely appreciate Dr. Wotkyns' support and kind remarks. I am assured by reviewing his algorithms that his comments are well founded on an in depth understanding of the complexity of such programs—even for the simplest aspects of operative treatment of colorectal cancer.

Relative to Dr. Cohn's comments: There are obvious variables I cannot control—the operating surgeon being one. Since the surgeon cannot be programmed, one must assume that his intraoperative assessment will be accurate and honest. It is hoped that by conscious consideration of the variables in question, in some selected situations, the surgeon might be directed towards a more appropriate response than would have been evolved from a situation in which the judgement variables are not verbalized. This program was not in operation when the reviewed cases were actually performed and, therefore, they were not influenced by myself or the computer program. The implications as to why there is a difference in responses between the various types of hospitals are clear. Whether or not we wish to face it, in the private setting there appears to be a more significant subconscious desire to produce a live patient with no complications and no colostomy; often to the detriment of the patient's immediate or long-term survival. Awareness of this possibility might improve the survival of some patients with colorectal cancers.

We have studied 800 cases with this program in four different hospital settings and locations. The results have been identical to the ones presented today. The program is not only consistent, but extremely reliable. The universal "it cannot be done" attitude towards programming clinical judgement is invalid. This program represents one very small example of how judgement decisions can be computerized and made much more objective. The value of this type of program for teaching is clear. The clinical application of this program, although not easily implemented, might improve the care of some patients with colorectal cancers.

Management of Pancreatic Trauma

RONALD C. JONES, M.D.

From the University of Texas
Health Science Center,
Dallas, Texas

Since 1950, 300 patients sustaining pancreatic injuries have been managed. Three-fourths of the injuries were due to penetrating trauma with a 20% mortality and one-fourth due to blunt trauma resulting in an 18% mortality. The pancreatic injury was responsible for death in only 3% of patients. Early onset of shock resulted in a 38% mortality whereas only 4% of normotensive patients died. No patient died of an isolated pancreatic injury. Sepsis was the second most common cause of death following hemorrhage. Preoperative serum amylase was elevated more frequently following blunt trauma than penetrating trauma, but did not correlate with injury.

There has been a tendency toward more frequent use of distal pancreatectomy for simple penetrating injuries without obvious ductal violation which increases operative time, blood loss and possible intra-abdominal abscess since resection usually requires splenectomy. Patients considered for an 80% distal resection are better managed with a Roux-en-Y limb to the distal pancreas since three patients developed diabetes following an 80% or greater resection. A conservative approach consisting of Penrose and sump drainage is adequate for most injuries.

DURING THE PAST TEN YEARS at Parkland Memorial Hospital at Dallas, there has been a 25% increase in pancreatic injuries over the previous decade. The frequency of blunt trauma has almost doubled, and accounted for one-third of the injuries seen in the last seven years.

Materials and Methods

During the past 27 years, 300 patients sustaining pancreatic trauma were reviewed. Their ages ranged from two to 76 years. There were 226 patients who received penetrating pancreatic injuries and 74 patients sustaining blunt trauma. These patients were analyzed for type and severity of injury, diagnosis, location, method of management, complications and mortality. All patients had a proven pancreatic injury determined at exploratory laparotomy.

Results

Diagnosis

Diagnosis included physical examination, peritoneal lavage, serum amylase determination and adequate surgical exploration. Indications for surgical exploration usually related to associated injuries. Isolated blunt trauma to the pancreas sometimes did not produce physical findings for 12–24 hours.

Serum Amylase Determination

Preoperative serum amylase determination was performed on 132 patients and was often elevated in less than two hours following injury. Elevation of amylase occurred in 71% of patients explored for blunt trauma, but in only 23% of patients sustaining penetrating pancreatic trauma. The longer the delay from injury to surgery, the more likely an elevation. Even with complete transection of the pancreas, the serum amylase was elevated in only 72% of 18 patients. Serum amylase elevation alone was not used as an indication for exploratory laparotomy in the absence of significant physical findings. These patients were admitted to the hospital and observed until the amylase returned to normal which usually occurred within 48 hours.

Associated Injuries

There were 154 patients (51%) who sustained retroperitoneal injuries in addition to pancreatic injury. Retroperitoneal injury occurred in 63% of patients following penetrating trauma, but in only 16% following blunt trauma. The pancreas was not often responsible for uncontrollable hemorrhage. When profuse bleeding occurred, the pancreas was mobilized and major retroperitoneal vessels were often the source of hemorrhage. There were 129 retroperitoneal vessel injuries

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests: Ronald C. Jones, M.D., Department of Surgery, The University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

0003-4932-78-0500-0555-0105 © J. B. Lippincott Company

TABLE 1. *Associated Injuries*

Penetrating (226 Pt.)		Blunt (74 Pt.)	
Liver	125	Liver	24
Stomach	117	Spleen	21
Colon	55	Duodenum	5
Duodenum	51	Kidney	4
Kidney	49	Gallbladder	4
Spleen	45	Colon	1
Small Bowel	37		0
Retroperitoneal vessels	129		6

including 21 aortic, 35 inferior vena cava, 14 superior mesenteric, 30 renal vessel and eight portal vein injuries. Associated colon injuries have increased following penetrating trauma to the pancreas with each decade from 15% in the first decade to 23% and subsequently to 32% in the third decade. Only one colon injury occurred following blunt trauma to the pancreas. These 56 colon injuries had a 34% mortality. Sepsis accounted for five of these 19 deaths and sepsis from the colon injury contributed to death in an additional five patients (Table 1).

Management of Pancreatic Injuries

Twenty-six patients died intraoperatively leaving 274 patients for postoperative evaluation. Penrose and sump drainage was instituted in 197 patients. Eight pancreatic fistulas and two pseudocysts developed. A major pancreatic fistula has previously been defined as one which drains in excess of one month. Of 23 deaths in these 197 patients, the pancreatic injury was the cause of death in only four. Intra-abdominal abscess developed in 16% managed by simple drainage (Table 2).

Method of Drainage

Penrose and sump drains were placed at the tip of the twelfth rib for direct drainage. Several patients were observed to have minimal pancreatic drainage for up to seven days, then had a significant increase in drainage. Since these injuries may drain from two to four weeks, the drains were left in place for ten days.

TABLE 2. *Pancreatic Trauma—Method of Management (274 Pt.)*

	Pt.	Fistula	Pseudo-cyst	Lesser Sac Abscess	Died
Drainage only	197	8	2	8	23
Distal pancreatectomy	30	2		1	1
Distal pancreatectomy and Roux-en-Y	22			1	5
Roux-en-Y—both ends	6				1
Roux-en-Y ant. over inj.	9			2	1
Roux-en-Y to head/CD	1				
Pancreaticoduodenectomy	7				3
No drainage	2		1		

Distal Pancreatectomy

Fifty-six patients underwent distal pancreatectomy, 22 had a Roux-en-Y limb placed to the end of the proximal pancreas and 30 had resection alone. Four patients died intraoperatively while undergoing a distal pancreatectomy. Two of 30 patients without a Roux-en-Y limb developed a major pancreatic fistula, one following penetrating and one after blunt trauma. There was one death from sepsis. Eighteen (60%) of these 30 patients having distal pancreatectomy developed an infection of which 11 (37%) were intra-abdominal abscesses. There were seven associated colon injuries in the 30 patients.

No fistula or pseudocyst developed in the 22 patients who had distal pancreatectomy and Roux-en-Y pancreaticojejunostomy. Roux-en-Y pancreaticojejunostomy was initially advocated for blunt injury to prevent a pancreatic fistula when there was associated contusion to the head of the pancreas. However, 14 patients had Roux-en-Y drainage following resection for penetrating trauma. Five deaths occurred among the 22 patients including one each from aspiration, occluded tracheostomy, myocardial infarction, closed head injury and sepsis from a leaking pancreaticojejunostomy.

Distal pancreatectomy has been used with increasing frequency in the past ten years for penetrating pancreatic trauma. Although the frequency of gunshot wounds to the pancreas increased only from 64 to 74%, the frequency of distal pancreatectomy increased from 7% prior to 1960 to 37% after 1970.

Pancreatic duct injury was occasionally determined during surgery by cholangiography, catheterization of the pancreatic duct through the duodenum if the duodenum had been ruptured, or by transecting the distal pancreas and pancreatogram. To avoid unnecessary blood loss while performing a distal pancreatectomy, sutures were placed in the superior and inferior borders of the pancreas, approximately 2 cm from the edge. Placement of these sutures along with isolation of the splenic vessels during distal pancreatectomy prevented unnecessary blood loss and provided better visualization. A splenectomy was almost always necessary. The cut edge of the pancreas was beveled in a fish-mouth fashion, enabling better closure using permanent suture material. When possible, the pancreatic duct was ligated.

Roux-en-Y to Both Ends of Pancreas

Six patients had complete transection of the pancreas secondary to blunt trauma, managed with implantation of both ends of the pancreas into a Roux-en-Y limb. One 76-year-old patient died from renal failure, cirrhosis and continued bleeding. This operation suggested by Jones and Shires in 1965 was to prevent pancreatic fistula, diabetes, pancreatic insufficiency and extensive pancreatic resection.[14] The procedure was used when 80% or more of the pancreas would have required resection.

Roux-en-Y to Anterior Surface of Pancreas

Nine patients had a Roux-en-Y limb to the surface of the pancreas over the site of injury. Four patients developed sepsis, including two right subphrenic abscesses, both associated with liver and colon injuries. A third patient developed a lesser sac abscess and bled into the Roux-en-Y from autolysis of the distal pancreas. The fourth patient developed retroperitoneal sepsis and bleeding and died following placement of a Roux-en-Y limb over a stellate fracture of the head of the pancreas. A significant pancreatic fistula developed in one patient draining up to 2000 cc per day, but closed in less than one month. The Roux-en-Y limb placed over the site of injury was more successful for injuries which had the posterior pancreatic capsule intact, but was associated with a high morbidity.

Avulsion Injuries

Avulsion of the common duct and ampulla from the duodenum occurred in three patients secondary to blunt trauma and all survived. Two patients underwent pancreaticoduodenectomy and one had placement of a Roux-en-Y limb to the ampulla and pancreas with closure of the duodenum. This patient developed a duodenal fistula requiring reoperation and drainage. With suspected injuries of the intrapancreatic portion of the common duct or ampulla, the common duct was opened proximally, a cholangiogram was performed and a catheter was passed into the duodenum. A number 10 Foley catheter was frequently inserted as a duodenostomy tube for decompression.[13]

Pancreaticoduodenectomy

Seven patients underwent pancreaticoduodenectomy. In two additional patients, pancreaticoduodenectomies were attempted, but died intraoperatively from major vessel injury. Five of seven pancreaticoduodenectomies followed gunshot wounds and three patients died. One died from sepsis secondary to a leaking choledochojejunostomy, one from hemorrhage and one of renal failure and sepsis with an associated colon injury. Both patients undergoing pancreaticoduodenectomy for blunt trauma survived.

TABLE 3. *Combined Penetrating Injury Duodenum and Head Pancreas (39 Pt.)*

			Complications		
	# Pt.	Died	Sepsis	Pancreatic Fistula	Duodenal Fistula
Drainage only	26	3	3	1	1
Pancreatico-duodenectomy	3	2			
Distal pancreatectomy	2				
Roux-en-Y to injury	1				
Postoperative mortality	32	5 (16%)			
Died during surgery	7	7			
Overall mortality	39	12 (31%)			

Combined Pancreaticoduodenal Injuries

Combined pancreaticoduodenal injuries occurred in 56 (19%) of patients with 25% mortality. Of 14 deaths in these 56 patients, ten were due to hemorrhage and four to sepsis. No patient died of the duodenal injury and only two patients died of the pancreatic injury.

There were 39 patients sustaining penetrating injury to the duodenal "C" loop and head of the pancreas, a more difficult problem of management. The overall mortality of these 39 patients was 31%, seven of whom died intraoperatively of major vessel injury (Table 3). Drainage alone was instituted in 26 of these patients and three died. One died of hemorrhage, another of renal failure and confluent lung abscesses and the third died from the combined injury with a peripancreatic abscess resulting in recurrent retroperitoneal hemorrhage. Complications included a major pancreatic fistula, a duodenoureteral fistula, and three intra-abdominal abscesses, but all survived. Pancreaticoduodenectomy was attempted in five patients, but two died intraoperatively from hemorrhage and two died postoperatively.

Combined pancreaticoduodenal injuries occurred in five patients following blunt trauma and were successfully treated. Two had a pancreaticoduodenectomy, two a Roux-en-Y limb to the injury and one a Roux-en-Y to both ends of the pancreas.

Complete Transection of Pancreas

Twenty-six patients had complete transection of the pancreas from blunt trauma, three of whom died intraoperatively of associated injuries. Of the remaining 23 patients, eight had a distal pancreatectomy, seven underwent distal pancreatectomy and a Roux-en-Y to the proximal pancreas and six had a Roux-en-Y to both ends of the pancreas. Two underwent pancreaticoduodenectomy (Table 4).

TABLE 4. *Transection Pancreas Blunt Trauma*

	Pt.	Died
Distal pancreatectomy	8	3
Resection with Roux-en-Y	7	3
Roux-en-Y both ends	6	1
Pancreaticoduodenectomy	2	
No Rx—Died During Surgery	3	3
Total	26	10 (38%)

Isolated Pancreatic Injury

There were 24 isolated pancreatic injuries, 18 from blunt trauma, including six complete transections, and six from penetrating injuries of which five were stabwounds and one gunshot wound. Isolated pancreatic injuries occurred in 24% of patients sustaining blunt trauma. One wound infection followed blunt trauma. No patient died of an isolated pancreatic injury.

Complications

Fistula and Pseudocyst

Ten patients developed major pancreatic fistulas, five associated with injuries to the head of the pancreas, four to the body, one to the tail, but none required reoperation. Pseudocysts developed in three patients early in the series, but none have occurred since 1963 or in the last 237 pancreatic injuries. This is a result of thorough visualization of the pancreas at surgery. Isolated penetrating pancreatic injury resulted in two major pancreatic fistulas and two lesser sac abscesses.

Diabetes

The normal pancreas is approximately 12–15 cm in length. Eight patients had from 11.5 to 13.5 cm of pancreas resected, as measured by pathology examination. This was an 80% or greater resection. Three patients developed diabetes. Two required insulin, one 50 units NPH daily and a second 35 units NPH daily. The third patient had a fasting blood sugar of approximately 200 mg% with a negative urine sugar. A fourth, following a 12 cm resection, had a slightly elevated FBS and a fifth had a slightly abnormal glucose tolerance test following a 13 cm resection.

TABLE 5. *Complications (267 Pt.)*

	No. Pt.	Colon Inj.	Died	Mortality
Abscess				
Lesser sac	12	2	3	25%
Subphrenic	29	13	5	17%
Intraabdominal	17	9	6	35%
Drain tract	27	10	1	4%
Wound infection	21	8		
Bacteremia (72–77)	11	4	5	45%

Pancreatitis

Five patients developed hemorrhagic pancreatitis, four of whom died. In three, the pancreatitis became evident by hemorrhage from the drain tract.

Sepsis

Excluding intraoperative deaths and those 24 hours postoperative, infection, including wound, drain tract and intra-abdominal abscess developed in 92 (34%) of 267 patients. Sepsis was the second most common cause of death following hemorrhage. Infection developed in 35% of patients sustaining penetrating trauma and in 32% following blunt trauma. The wound infection rate was 8%, however, several wounds were left open due to colon injury. Intra-abdominal abscess occurred in 20% of 267 patients and 24% died. In the past seven years, septicemia was documented in 11 patients with a 45% mortality.

The most common organisms cultured from blood and intra-abdominal abscesses were Enterococcus, Klebsiella, *E. Coli*, and *Bacteroides fragilis*. The incidence of infection has increased during the last ten years in spite of preoperative antibiotics. Intra-abdominal abscess occurred in 23% of patients during the past ten years, but in only 16% prior to that time when antibiotics were used in approximately one-half of cases. However, severity of injury and resuscitative measures in the field could not be evaluated.

Sepsis was related to shock. Sixty-three per cent of patients who developed sepsis had been in shock. Of 106 patients in hemorrhagic shock who lived 24 hours, 31% developed infection, whereas, of 158 normotensive patients, only 12% became infected.

Gastrointestinal injury or opening the gastrointestinal tract to perform jejunostomy, gastrostomy or a Roux-en-Y procedure occurred in 194 (73%) patients. Thirty-seven patients developed either subphrenic or intra-abdominal abscesses. Nineteen (51%) were associated with colon injury and 30 (80%) were associated with bowel injury or intraoperative opening of the gastrointestinal tract (Table 5).

The appropriate side for a subphrenic abscess to develop correlated closely with liver or spleen injury. Twenty-four of 26 subphrenic abscesses were associated with liver or spleen injury and 20 had gastrointestinal contamination. Of 24 patients with liver and spleen injuries who subsequently developed subphrenic abscess, 21 of the 24 occurred on the appropriate side of the liver or spleen injury. Of those patients develop-

TABLE 6. *Pancreatic Trauma 1950–1977*

	Pt.	Died	Mortality
Penetrating	226	46	20%
Stab	46	3	7%
Gunshot	156	29	19%
Shotgun	24	14	58%
Blunt	74	13	18%
Total	300	59	20%

ing intra-abdominal abscesses, 11 of 12 had both gastrointestinal tract contamination and spleen or liver injuries. Colon injury was more frequently associated with subphrenic and intra-abdominal abscess than with lesser sac abscess, indicating the pancreatic injury was a contributing factor to the development of peripancreatic abscesses.

Mortality

Type of Injury

The overall mortality has remained near 20%, reflecting not only the pancreatic injury, but also the mortality of severe abdominal trauma. Missile injuries accounted for 60% of the injuries. Only three of 46 patients died of a stab wound to the pancreas, none in the past ten years, and these were unrelated to the pancreatic injury. Stab wounds resulted in a 7% mortality, gunshot wounds 19% and shotgun wounds 58%. The mortality for blunt trauma was 18% (Table 6).

Of 226 penetrating pancreatic injuries, 17 (8%) were secondary to attempted suicide with a 35% mortality. The mortality for penetrating injuries to the pancreas has steadily increased with each decade (Table 7).

Location of Injury

The mortality of penetrating trauma is highest with injuries to the head of the pancreas. Mortality of blunt trauma related to complete transection at the neck reflecting retroperitoneal vessel injury (Table 8).

TABLE 8. *Pancreatic Trauma—Location*

	Pt.	Died	Mortality
Penetrating			
Head	77	21	27%
Body	94	21	22%
Tail	55	4	7%
Blunt			
Head	30	4	13%
Body	35	8	23%
Tail	9	1	11%

Shock

Mortality correlated closely with shock. Forty-seven per cent of patients were in shock preoperatively or intraoperatively. Their mortality was 38% in contrast to a 4% mortality for normotensive patients. Of those patients who died, 88% had been in shock following injury.

TABLE 7. *Pancreatic Trauma—Mortality*

	Penetrating		Blunt	
1950–1959	6/43	14%	3/5	60%
1960–1969	18/96	19%	3/27	11%
1970–1977	22/87	25%	7/42	17%

Cause of Death

Of the 59 patients who died, 26 were intraoperative. An additional 11 patients died within 48 hours from hemorrhage, aspiration, or head injury. Of the remaining 22 patients, four died of pulmonary complications, four from head injury, and one myocardial infarction. Nine died of the pancreatic injury, often associated with sepsis, stress bleeding, renal failure, and hemorrhagic pancreatitis. There were two deaths from renal failure secondary to severe hemorrhage. The nine deaths due to pancreatic injury were associated with injuries to the head of the pancreas, six from gunshot wounds, and three secondary to blunt injury (Table 9).

Discussion

In a review of 1091 cases of pancreatic trauma from institutions reviewing greater than 50 cases, the mortality for penetrating pancreatic trauma was 23% and 18% for blunt trauma with an overall mortality of 21% (Table 10).[3,12,20,22,24,25,27–29] Mortality is related to the location of the pancreatic injury, shock and associated injuries. Thompson reported a 30% mortality in injuries to the head of the pancreas.[24] Patients in shock have 28% to 61% mortality versus normotensive patients with a 4–9% mortality.[22,29]

Olsen noted that one-third of patients with a preoperative elevation of serum amylase had no significant intra-abdominal injury.[17] Moretz found no correla-

TABLE 9. *Deaths (59 Pt.)*

Primary		Contributing	
Hemorrhage	34	Renal failure	7
Pancreatic injury and sepsis	9	Pulmonary	4
Abdominal sepsis	4	Pancreatitis	1
Head injury	4		
Pulmonary	5		
Renal Failure	2		
Cardiac (M.I.)	1		

TABLE 10. *Summary of Ten Series of Pancreatic Trauma*

Author	Review Period	Patients Operated	Pene-trating	Deaths	Blunt	Deaths	Overall Mortality
Walters	1939–63	131	73	15	58	9	18%
Jordan	1940–67	140	117	23	23	2	18%
Stone	1948–61	62	56	12	6	1	21%
Thompson	1948–63	73	39	10	34	4	17%
Jones	1950–77	300	226	46	74	13	20%
Freeark	1952–61	82	59	10	23	5	17%
Blaisdell	1952–68	56	33	10	23	6	29%
Walt	1956–65	84	45	12	39	15	32%
Heitsch	1963–74	100	77	27	23	2	29%
White	1965–71	63	36	5	27	1	10%
Total		1091	751	170 (23%)	330	58 (18%)	21%

tion between pancreatic injury or its severity and amylase elevation following blunt trauma.[16] Serum amylase can neither identify nor exclude serious pancreatic injury and is not used as an indication for celiotomy. When elevated, the pancreaticoduodenal area is carefully examined.

If upper abdominal retroperitoneal injury is suspected preoperatively following blunt trauma, and the patient has minimal physical signs, a gastrografin gastrointestinal series is obtained. During abdominal exploration, demonstration of retroperitoneal hematoma, crepitation, or bile requires mobilization of the duodenum and head of the pancreas. The lesser sac is opened through the gastrocolic ligament and the pancreas is examined. The pancreas is not extensively mobilized unless resection is contemplated. Mobilization may further devascularize the pancreas and contribute to necrosis which possibly occurred in two cases in this series. A cholangiogram is performed if there is question of injury to the common duct.

Untreated disruption of the pancreatic duct has been the main source of morbidity associated with pancreatic injury.[2] If pancreatic duct injury is suspected, a pancreatogram may be necessary. Prior to extensive pancreatic resection, definite ductal injury is proven. Gougeon has advocated transduodenal pancreatography using the fiberoptic duodenoscope intraoperatively to determine ductal injury.[11] This would require expertise and rapid availability to be of value in the critically ill patient.

Appropriate management of a pancreatic injury is determined by its severity, associated organ injury, and condition of the patient. Most are treated by drainage. During the past decade, more aggressive treatment has been advocated, including various Roux-en-Y drainage procedures and pancreaticoduodenectomy.[14,15,19] The incidence of pancreatic fistula and pseudocyst has declined due to more frequent resection, but mortality has increased perhaps due to more severe injury, but also to overly enthusiastic resection.

For simple contusion or laceration and no recognized major ductal injury, Penrose and sump drainage has been adequate. This method of management has been demonstrated to reduce morbidity and mortality of pancreatic trauma.[3,10,22] Sump drainage protects the skin, prevents digestion of intestinal anastomosis and retroperitoneal vessels and prevents accumulation of pancreatic juice in the lesser sac. Drainage has been a successful method of managing penetrating injuries of the head of the pancreas unless resection was necessitated by uncontrollable hemorrhage or a shattered pancreas and duodenum.

Distal pancreatectomy is an effective method of treating injury to the body and tail of the organ, since traumatized and devitalized tissue is removed and postoperative fistula and pseudocyst formation are decreased.[29] However, the incidence of subphrenic abscess was increased in patients undergoing distal pancreatectomy and splenectomy. Complete ductal disruption of the body and tail of the pancreas to the left of the superior mesenteric vessels requires resection.

With injuries to the right of the superior mesenteric vessels, internal drainage is indicated to preserve pancreatic function which may be lost with resection of 80% or 12 cm of pancreas. A Roux-en-Y limb with implantation of one or both ends of the pancreas may take little more time than distal resection with splenectomy.[14,15] This method leaves all functioning pancreatic tissue, therefore, avoiding the possibility of pancreatic insufficiency or diabetes which has also been reported by Freeark and Bach.[2,9] Yellin reported eight cases of pancreatic injury in which 13 cm or more of pancreas was resected and one patient developed diabetes.[32] In addition to these four reported cases of diabetes, Rienhoff reported pancreatic insufficiency following extensive pancreatic resection.[18]

Yasugi demonstrated in dogs following greater than 88% pancreatectomy, hyperglycemia occurred immediately but did not occur with less than 70% resection.[30] However, hyperglycemia did not occur following resections of 70–88% until six weeks to seven months. Secretion of glucagon from the remnant of the pancreas was well maintained but the secretion of insulin was easily impaired after major resection of the pancreas. This would indicate that the diabetes might not be detected during hospitalization for the injury as happened in some patients in this series.

Although the frequency of gunshot wounds at Parkland Memorial Hospital has only increased 10% in the past decade, the frequency of distal resection has increased from 7% in the preceding 17 years to 37%. Blaisdell reported an increase in use of distal pancreatectomy from 27 to 42% during a four year period compared to the previous 16 years.[21] Whether or not this represents a true increase in severity of injuries justifying resection is difficult to determine. If the patient has a questionable ductal injury and is unstable, drainage is the treatment of choice. Extensive pancreatic resection is not undertaken for questionable ductal injury. Removal of major portions of this relatively inaccessible and highly vascular organ is a formidable undertaking in what is often a desperately ill patient.[10]

A Roux-en-Y to the proximal end of the pancreas following distal resection is occasionally indicated in the presence of severe associated contusion of the head to prevent pancreatic fistula and pseudocyst. It is almost never indicated following penetrating trauma. Utilization of a sump drain is essential when anastomosing bowel to pancreas.

For combined pancreaticoduodenal injuries, several methods of management are available, including diverticulization, pancreaticoduodenectomy, Roux-en-Y limb and simple drainage. Donovan has advocated closure of the duodenal perforation with accompanying vagotomy, antrectomy with gastrojejunostomy, gastrostomy, duodenostomy and choledochostomy when indicated for combined pancreaticoduodenal injuries.[6] This is an attempt to defunctionalize a duodenal perforation, decrease pancreatic stimulation with vagotomy and antrectomy, and prevent a lateral duodenal fistula with a duodenostomy. Mortality for nine patients so treated was 33%, the same as that reported for pancreaticoduodenectomy.[6] Donovan recently reported a mortality of only 16% for this diverticulization procedure; however, in over half the injuries, there was no demonstrable pancreatic injury, thus only duodenal injuries were treated, which is not a comparable group.[4]

Eighty-one patients have been reported who had a pancreaticoduodenectomy with a 33% mortality.[1,2,5,8,12,28,31] When separated, the mortality following pancreaticoduodenectomy for blunt trauma was 26%, but increased to 37% for penetrating injury. The overall condition of the patient and associated injuries must be considered prior to submitting a patient to several hours of surgery. There are times when pancreaticoduodenectomy is necessary, but they are rare. Strict indications for pancreaticoduodenectomy include combined pancreaticoduodenal injuries in which the duodenum cannot be repaired or is nonviable, or uncontrollable hemorrhage from the duodenum or pancreas. In addition to fistula and abscesses, marginal ulceration with upper gastrointestinal bleeding has occurred following pancreaticoduodenectomy in which a vagotomy or adequate subtotal gastric resection was not performed. Symptoms of dumping, diabetes, weight loss, and diarrhea have occurred.[26]

Thal and Fish reported the successful management of avulsion of the ampulla from the duodenum.[7,23] If the duodenum is viable, this injury may be treated with closure of the duodenum and a Roux-en-Y anastomosis to the avulsed ampulla of Vater, but may require pancreaticoduodenectomy. Freeark reported the successful anastomosis of the pancreatic duct to the anterior duodenum.[9]

Jordan found pancreatic fistula to be the most common complication following operative therapy, occurring in 35% of cases usually following blunt trauma.[27] In the PMH series, six major pancreatic fistulas followed penetrating injuries and four followed blunt trauma. Continuous suction with sump drainage is necessary to prevent skin maceration and to obtain accurate estimates of fluid loss.[3] Vigorous fluid replacement with balanced salt solution is indicated. Elevation of the serum amylase is frequent in the presence of a draining pancreatic fistula representing transperitoneal absorption. Elevation of the serum amylase in the absence of pancreatic fistula may indicate the development of pancreatic pseudocyst.

Summary

If there is no obvious major ductal disruption following penetrating injury to the head of the pancreas, sump and Penrose drainage is preferable treatment rather than extensive distal resection or pancreaticoduodenectomy. For those injuries requiring less than 80% resection, Roux-en-Y drainage of the remaining pancreas is rarely indicated. Injuries which would require 80% or greater resection are better managed with a Roux-en-Y to the distal pancreas, following proven injury to prevent diabetes and pancreatic insufficiency. Roux-en-Y drainage to the site of major ductal injury without resection has resulted in a high morbidity.

Sepsis has become a significant cause of death and morbidity and appears to be related to shock, and

gastrointestinal injury or unnecessary opening of the gastrointestinal tract in a previously uncontaminated abdomen. Contamination in association with liver and spleen injury results in a high incidence of intra-abdominal abscess formation.

Although several methods of management have been advocated for pancreatic trauma, most important is identification of ductal injury at the initial operation and institution of appropriate definitive treatment. When a pancreatic injury is identified, the method of management is determined by the condition of the patient, the severity of injury and anatomic location.

References

1. Anane-Sefah, J., Norton, L. W. and Eiseman, B.: Operative Choice and Technique Following Pancreatic Injury. Arch. Surg., 110:161, 1975.
2. Bach, R. D. and Frey, C. F.: Diagnosis and Treatment of Pancreatic Trauma. Am. J. Surg., 121:20, 1971.
3. Baker, R. J., Dippel, W. F., Freeark, R. J. and Strohl, E. L.: The Surgical Significance of Trauma to the Pancreas. Arch. Surg., 86:180, 1963.
4. Berne, C. J., Donovan, A. J., White, E. J. and Yellin, A. E.: Duodenal "Diverticulization for Duodenal and Pancreatic Injury. Am. J. Surg., 127:503, 1974.
5. Chambers, R. T., Norton, L. and Hinchey, E. J.: Massive Right Upper Quadrant Intra-abdominal Injury Requiring Pancreaticoduodenectomy and Partial Hepatectomy. J. Trauma, 15:714, 1975.
6. Donovan, A. J. and Hagen, W. E.: Traumatic Perforation of the Duodenum. Am. J. Surg., 111:341, 1966.
7. Fish, J. C. and Johnson, G. L.: Rupture of Duodenum Following Blunt Trauma: Report of a Case with Avulsion of Papilla of Vater. Ann. Surg., 162:917, 1965.
8. Foley, W. J., Gaines, R. D. and Fry, W. J.: Pancreaticoduodenectomy for Severe Trauma to the Head of the Pancreas and the Associated Structures: Report of Three Cases. Ann. Surg., 170:759, 1969.
9. Freeark, R. J., Corley, R. D., Norcross, W. J. and Baker, R. J.: Unusual Aspects of Pancreatoduodenal Trauma. J. Trauma., 6:482, 1966.
10. Freeark, R. J., Kane, J. M., Folk, F. A. and Baker, R. J.: Traumatic Disruption of the Head of the Pancreas. Arch. Surg., 91:5, 1965.
11. Gougeon, F. W., Legros, G., Archambault, A., et al.: Pancreatic Trauma: A New Diagnostic Approach. Am. J. Surg., 132: 400, 1976.
12. Heitsch, R. C., Knutson, C. O., Fulton, R. L. and Jones, C. E.: Delineation of Critical Factors in the Treatment of Pancreatic Trauma. Surgery, 80:523, 1976.
13. Jones, R. C., McClelland, R. N., Zedlitz, W. H. and Shires, G. T.: Difficult Closures of the Duodenal Stump. Arch. Surg., 94:696, 1966.
14. Jones, R. C. and Shires, G. T.: The Management of Pancreatic Injuries. Arch. Surg., 90:502, 1965.
15. Letton, A. H. and Wilson, J. P.: Traumatic Severance of Pancreas Treated by Roux-Y Anastomosis. Surg. Gynecol. Obstet., 109:473, 1959.
16. Moretz, J. A., III, Campbell, D. P., Parker, D. E. and Williams, G. R.: Significance of Serum Amylase Level in Evaluating Pancreatic Trauma Am. J. Surg., 130:739, 1975.
17. Olsen, W. R.: The Serum Amylase in Blunt Abdominal Trauma. J. Trauma, 13:200, 1973.
18. Rienhoff, W. F. and Donahoo, J. S.: Isolated Complete Rupture of the Pancreas from Non-penetrating Abdominal Trauma, Treated by Distal Resection. Am. Surg., 33:148, 1967.
19. Salyer, K. and McClelland, R. N.: Pancreatoduodenectomy for Trauma. Arch. Surg., 95:636, 1967.
20. Sheldon, G. F., Cohn, L. H. and Blaisdell, F. W.: Surgical Treatment of Pancreatic Trauma. J. Trauma, 10:795, 1970.
21. Steele, M., Sheldon, G. F. and Blaisdell, F. W.: Pancreatic Injuries. Arch. Surg., 106:544, 1973.
22. Stone, H. H., Stowers, K. B. and Shippey, S. H.: Injuries to the Pancreas. Arch. Surg., 85:525, 1962.
23. Thal, A. P. and Wilson, R. F.: A Pattern of Severe Blunt Trauma to the Region of the Pancreas. Surg. Gynecol. Obstet., 119: 773, 1964.
24. Thompson, R. J., Jr. and Hinshaw, D. B.: Pancreatic Trauma: Review of 87 Cases. Ann. Surg., 163:153, 1966.
25. Walters, R. L., Gaspard, D. J. and Germann, T. D.: Traumatic Pancreatitis. Am. J. Surg., 111:364, 1966.
26. Warren, K. W., Poulantzas, J. K. and Kune, G. A.: Life After Total Pancreatectomy for Chronic Pancreatitis. Ann. Surg., 164:830, 1966.
27. Werschky, L. R. and Jordan, G. L.: Surgical Management of Traumatic Injuries to the Pancreas. Am. J. Surg., 116:768, 1968.
28. White, P. H. and Benfield, J. R.: Amylase in the Management of Pancreatic Trauma. Arch. Surg., 105:158, 1972.
29. Wilson, R. F., Tagett, J. P., Pucelik, J. P. and Walt, A. J.: Pancreatic Trauma. J. Trauma, 7:643, 1967.
30. Yasugi, H., Mizumoto, R., Sakurai, H. and Honjo, I.: Changes in Carbohydrate Metabolism and Endocrine Function of Remnant Pancreas after Major Pancreatic Resection. Am. J. Surg., 132:577, 1976.
31. Yellin, A. E. and Rosoff, L.: Pancreatoduodenectomy for Combined Pancreatoduodenal Injuries. Arch. Surg., 110: 1177, 1975.
32. Yellin, A. E., Vecchione, T. R. and Donovan, A. J.: Distal Pancreatectomy for Pancreatic Trauma. Am. J. Surg., 124:135, 1972.

DISCUSSION

DR. GEORGE L. JORDAN, JR. (Houston, Texas): This paper is of significance, because only 20 years ago pancreatic trauma was rare, and when we first reviewed our experience, we were seeing only two or three cases a year. Currently, we see about 40 cases a year, and I recently had reason to review a series of cases similar in size to that reported by Dr. Jones.

Through these 20 years, many papers have been published on small groups of cases, and many techniques were developed. It is only, however, when a series such as Dr. Jones' is analyzed in detail that the overall problem can be assessed so that relatively definitive conclusions are possible. We are indebted to Dr. Jones for this fine presentation today, and I urge all of you interested in the subject to read his total manuscript in detail.

I would like to emphasize the point that he last made; namely, that conservatism really is the keynote of the treatment of pancreatic trauma. That doesn't mean that resection is never indicated. In many instances, resection is mandatory because of devitalization of the pancreas, and the Whipple operation and even total pancreatectomy may be necessary. On the other hand, most of the patients can be treated by drainage or by reconstruction with a Roux-en-Y loop.

I have reviewed 56 cases of total transection of the pancreas, both from penetrating and blunt trauma, and our lowest mortality rate has been in those treated conservatively. This is partly, of course, because of the severity of trauma which necessitated resection; but we have had no deaths among the patients who were treated by Roux-en-Y drainage of the caudal end of the pancreas.

I do not believe that we need to drain both ends. The proximal end can be closed and the distal end drained into the Roux-en-Y loop.

The mortality rate of pancreatic trauma is primarily related to multiple organ injury; and as indicated in this paper, most of the deaths occur in the first 24 hours. In our own experience, as in his, if only the pancreas is injured or no more than two other organs, the mortality rate is quite low. In a recent series of 100 cases that I reviewed, our overall mortality rate, fortunately, had been reduced to 14%.

The pancreas is rarely the cause of death immediately, and thus, in general, in a patient with multiple injuries, the pancreas should be treated last. It rarely causes massive hemorrhage from the pancreas *per se*. Severe hemorrhage is from the major vessels in close proximity. Thus, in general, one will treat the other lesions first and the pancreas last. If the patient is unstable, I agree completely that one may just drain the pancreas.

On the other hand, when the patient is stable, there are multiple procedures which one may choose, and it's only with this type of review that we can choose the best procedure for each individual patient.

DR. FRANK C. SPENCER (New York, New York): In reviewing experiences with pancreatic fistula following trauma at our staff conference at New York University about one and a half years ago, a review of published experiences found that in a series of 234 distal pancreatectomies, the frequency of pancreatic fistula varied from 13–30%. On closer analysis, the principal problem seems to be that of finding and securely closing the transected pancreatic duct. The problem was often compounded by hemorrhage in devitalized, contaminated tissue. The two questions that arose were: How to find the transected pancreatic duct and does the method of closure in this contaminated, devitalized field influence the frequency of fistula formation, considering the choices of an absorbable suture, silk or Dacron, or staples?

Dr. Leon Pachter in our Department of Surgery has investigated this problem in some detail in the past year and prepared the data showed on these three slides. In 12 patients undergoing distal pancreatectomy, the end of the transected pancreas has been closed with the stapling device. This is the standard TA-55 stapler, which inserts one row of 3.5 mm staples. As all of you know, we are all indebted to Dr. Mark Ravitch for introducing and popularizing the stapling concept in this country several years ago, with modifications of the techniques employed in Russia.

The crucial point in the use of the stapler is that it is applied to healthy pancreatic tissue. [Slide] Subsequently, the tissue beyond the staples is amputated but not oversewn. A drain is left in place for about five to eight days. With the nine cases, eight recovered uneventfully. One patient developed a fistula who had an associated injury of his portal vein, inferior vena cava and developed massive ascites following ligation of his portal vein. As Dr. Jordan previously indicated, much of the morbidity with pancreatic injuries is related to the associated injuries.

DR. JOHN L. CAMERON (Baltimore, Maryland): I believe this series of 400 or 500 patients with acute pancreatitis probably represents the largest group of well-studied patients with acute pancreatitis in this country. I think the ability to identify patients as the authors do as soon as they come into the hospital on the basis of prognostic signs as to whether they will have severe or mild pancreatitis is a very important contribution.

I certainly agree with Dr. Spencer and Dr. Ranson that there are a large group of patients, the majority of patients with acute pancreatitis, who will recover without any treatment. We have performed prospective randomized clinical trials in the last several years, evaluating antibiotic therapy and atropine therapy, and there has been a study from California evaluating the use of the nasogastric tube, and none of these modalities affect the course of acute pancreatitis in the over-whelming number of patients who present. And as Dr. Spencer stated, if you don't do anything to hurt the patient, the majority of them will recover.

However, there are a small group with a very high mortality, and I think that the present series of patients is the largest series of patients with severe pancreatitis treated with peritoneal lavage, and it gives us some hope of improving the survival in this group.

I know that Dr. Ranson some time ago started a prospective randomized trial evaluating the use of peritoneal lavage in severe episodes of pancreatitis, and I wonder if he would give us some details of that prospective study, and why it was terminated, since the data presented here, by and large, is retrospective analysis.

I rise mostly to discuss antibiotic therapy, however, in acute pancreatitis. We performed a study in 100 consecutive patients with acute pancreatitis several years ago, randomizing the use of ampicillin. Dr. John Sawyers presented a second study at this Association a year or two ago, again evaluating the use of ampicillin in acute pancreatitis. Both of our studies demonstrated that ampicillin was of no value in the treatment of acute pancreatitis, that the number of septic complications was not decreased, and those septic complications, when they occurred on ampicillin, were apt to be with resistent organisms.

I think this can be interpreted in one of two ways: either we used the wrong antibiotic, or else antibiotics should not be used. Ampicillin does not cover the majority of organisms that are responsible for causing pancreatic abscesses, and I wonder if the increase in late mortality, after the improvement in early mortality through peritoneal lavage, could not be decreased if, instead of ampicillin, possibly an aminoglycoside along with penicillin and clindamycin, or an aminoglycoside along with chloromycetin, were used, either prophylactically, parenterally, or, maybe even better yet, in the dialysis fluid.

Finally, I'd like to make one last comment. I think that the data available from the literature suggest that the Levin tube does not play a major role in influencing the course or the outcome, of acute pancreatitis. I think most large series of pancreatic abscesses demonstrate that there are two periods in which abscesses occur: either immediately, in a very severe case in which there is massive pancreatic necrosis, or in the period of two or three weeks after the initial presentation, after, presumably, an initial sterile piece of infarcted pancreas becomes suprainfected. And I would think that that's why his patients who initially improved and began eating subsequently developed a pancreatic abscess, and that it was probably unrelated to the onset of eating and the absence of Levin tube suction for 14 days.

DR. ERNEST F. ROSATO (Philadelphia, Pennsylvania): When there were two Rosatos at the University of Pennsylvania, we had a very active interest in the treatment of pancreatitis by lavage. We studied this first in the laboratory with guinea pigs and with dogs, and, interestingly, we found that lavage does improve survival when no other treatment was given; and, furthermore, it didn't particularly matter which way you administered it, either by operative placement of the catheter or by percutaneous placement.

When we applied this to humans, we used the operative placement of catheters because of Dr. Waterman's initial successes that had been reported the year before, and we treated approximately ten patients with an 80% survival. While we did not classify them according to this very nice classification, which was published a little bit later, the great majority, at least 80%, would have fallen within at least the 5 to 6 category, and several into the 7 to 8 category.

We had an 80% survival with the operative placement of catheters, and one thing we did was not to have a set period of time for lavage. We judged when to stop the peritoneal lavage by the amylase drainage from the catheter, and when it fell below 1000 units, we stopped lavage. We would then recheck it two days later, and if it were elevated again, we would begin lavage again. With this technique, we were required to treat some of the patients for as long as two to four weeks, and I think this might explain some of the late abscesses that are seen with this particular treatment modality.

I would like to ask Dr. Spencer what his end points were, and whether he thinks it would be worth a trial of this prolonged lavage, in view of the fact that the operative mortality remained quite high in this group of patients who do get operated upon.

DR. SAMUEL R. POWERS (Albany, New York): I would just like to raise a note of caution in discussing Dr. Jones' paper.

The group in Texas, has had an enormous experience in the recognition of pancreatic injury, and I think it's important to emphasize that those of us who don't see quite as large a number of cases may not recognize them easily, particularly in the presence of a retroperitoneal hematoma. Although it has been the teaching for a long time, and many surgeons still believe, that a stable, nonpulsatile retroperitoneal hematoma should be left alone, I would suggest that this is not the case, and that pancreatic injuries will be missed. We believe that all retroperitoneal hematomas above the level of the pelvic rim should be explored very carefully, because a missed pancreatic injury is a very bad injury indeed.

DR. RONALD C. JONES (Closing discussion): I know of no one more capable of discussing trauma than the group from Houston; and certainly Dr. Jordan speaks with experience. He's given us direction for the last 25 years in the approach to pancreatic trauma.

Implanting both ends of the pancreas into a Roux-en-Y limb is only advocated if extensive resection is required, and there is associated trauma or contusion to the head of the pancreas, which might result in pancreatic fistula from the proximal segment. Implanting the distal end of the pancreas into a Roux-en-Y limb, described by Dr. Letton, is otherwise a fast and acceptable procedure.

Dr. Spencer, the variation in incidence of pancreatic fistula in the literature, I think, relates to the definition utilized by many surgeons as to what constitutes a pancreatic fistula. We have arbitrarily defined it as a fistula which drains in excess of one month. However, there are some pancreatic fistulas that drain a shorter time, but with considerable volume.

Permanent suture material has always been used, rather than catgut, which might dissolve quickly in the presence of activated pancreatic juice. We do attempt to ligate the pancreatic duct, but I do not think that this will prevent a pancreatic fistula, because there are many smaller ducts which are not ligated at the time.

We attempt to fishmouth the distal end of the proximal pancreas and oversew this with permanent suture material. We have used both silk and proline, but have not analyzed it as to whether the incidence of fistula is more or less with either. Most will drain for at least two weeks.

I think the use of the stapler, as you outlined, is an excellent suggestion. It would probably give a much better closure of both major and minor pancreatic ducts, but I think the most important thing is to be certain that there is Penrose and sump drainage placed at the point of injury, so when a collection appears, there is suction to promptly relieve it and prevent the development of lesser sac abscesses.

The comments by Dr. Powers were certainly in order. Our review of retroperitoneal injuries following penetrating trauma indicated there were associated retroperitoneal injuries, in addition to the pancreatic injury in 63% of cases; whereas, following blunt trauma, they occurred in 16%.

We advocate exploration of all retroperitoneal hematomas, unless we are reasonably certain that we are dealing only with pelvic fracture, in which case we would leave the retroperitoneum closed.

DR. JOHN H. C. RANSON (Closing discussion): I'd like to thank the discussants for their comments. I particularly appreciate Dr. Rosato's comments, because the experimental and clinical studies of the Drs. Rosato stimulated our interest in evaluating peritoneal lavage in patients with severe pancreatitis.

Dr. Rosato commented that, in their experimental studies, it did not seem to matter whether the catheters were placed at operation or percutaneously, but I think that there's an important distinction between the experimental situation and the clinical situation. In the experimental studies, operation was required to induce pancreatitis, so that all of the animals had undergone laparotomy in any event. Dr. Rosato suggested leaving the catheters for longer periods of time. We have made an arbitrary cutoff at four days, principally because we have been worried about introducing infection into the peritoneal cavity around the catheter. His suggestion is well taken. It is possible that lavage would be more effective if we were bolder about leaving the catheters longer.

There are a couple of technical hazards of lavage which I think should be emphasized. The first is that most of these patients have severe respiratory distress, and the addition of 2 l. of additional peritoneal fluid may cause a significant deterioration in their respiratory status. Therefore, pulmonary function needs to be closely monitored and, in a number of instances, it has been necessary to decrease the volume and timing of the cycle to avoid undue respiratory problems. The second potential hazard is that the tonicity of the lavage fluid is maintained with glucose. Since impaired glucose tolerance is a feature of severe pancreatitis, quite marked hyperglycemia has occurred in some patients during lavage, and glucose levels need to be closely monitored.

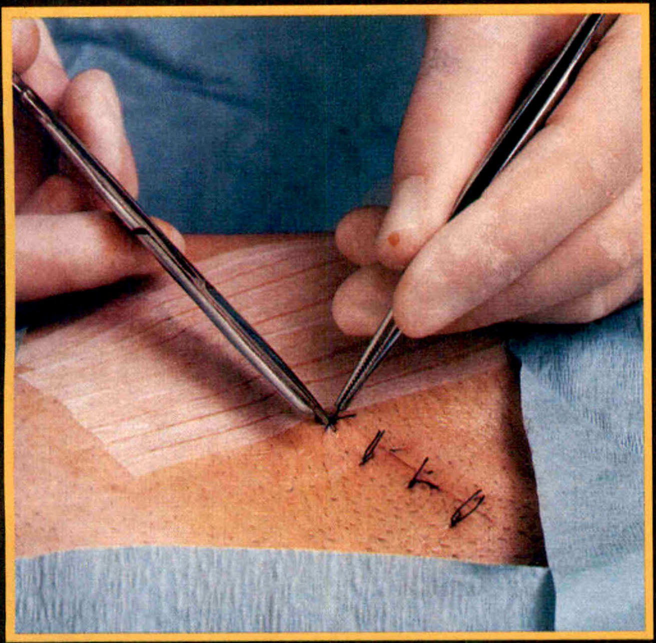
Dr. Cameron, you questioned our use of antibiotics, and following your study and that of Dr. Sawyers, our plan has been to administer antibiotics to patients until the 48 hour evaluation period is over. In patients who have less than three signs, the antibiotics are then stopped. The two studies, yours and Dr. Sawyers', both primarily involved patients who had rather mild acute alcoholic pancreatitis. The efficacy of antibiotics in preventing late peripancreatic abscesses needs to be evaluated on a controlled basis in patients with more severe disease and those with biliary pancreatitis.

You asked about the randomized study. Our initial evaluation of lavage was in a randomized study that included five patients who were lavaged and five who were not. In that small study the periods of hyperamylasemia, leukocytosis, and hypocalcemia were quite markedly shortened in the lavaged group. The most important finding was that the mean period spent in the ICU was reduced from 17 days to eight days in the lavaged group. Finally, there was one death in a nonlavaged patient. The controlled trial was stopped because the next patient who came along had five signs after he had been in the hospital for 48 hours. At that time, he was deeply comatose. He was not hypovolemic, but had hypotension, with a blood pressure of 80 mm Hg, despite massive pharmacological support. He was anuric, and had an arterial Po_2 of 59 mm Hg in 100% oxygen with positive end expiratory pressure. Because of the dramatic early response that we had seen in the controlled trial, we couldn't persuade anybody to consider withholding lavage in this patient. Within a few hours of the institution of lavage, he began to make urine. The following day he was responsive to his name, and four days later, when lavage was discontinued, he was off the respirator, off all pharmacologic support of his blood pressure, and had no detectable neurologic deficit.

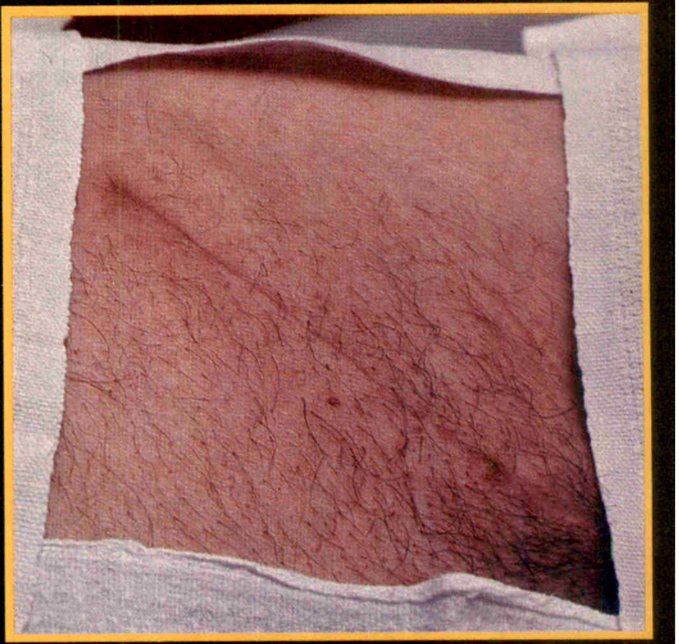
It was this type of patient, however, which brought us to consider the potential hazards of early feeding. This patient responded so dramatically that his nasogastric tube was removed, and oral feedings were resumed on the seventh hospital day. This was in contrast to a mean period NPO in patients with five signs of 21 days. About two days after he began feeding, this patient had a dramatic re-exacerbation of his disease, and developed late complications which eventually led to his death. We would have to agree with you that we don't know whether the early feeding produced this re-exacerbation or whether it would have occurred in any event. However, following the introduction of the arbitrary minimum period of fourteen days without oral feedings, there have been no deaths in the last nine patients treated with nonoperative lavage.

72-HOUR SUTURE REMOVAL

Replace sutures with STERI-STRIP® Skin Closures for enhanced wound healing, a finer scar, less chance of infection.[1]



Sutures removed 72 hours postoperatively.



38 days postop.

STERI-STRIP Brand Skin Closures make suture removal possible at a point that is most beneficial to the wound — 72 hours postoperatively.[2,3] The wound develops tensile strength faster due to the uniform stress applied to collagen fibers and fibrils, causing rapid fiber orientation.[4] When sutures are removed early STERI-STRIP Skin Closures provide firm support, reduced suture effects and greater patient comfort.

Contact your 3M Surgical Products representative for further information. 3M Surgical Products Division, 3M Center, St. Paul, MN 55101.

REFERENCES:

1. Edlich RF, Rodeheaver G, Kuphal J, deHoll JD, *et al:* Technique of closure: Contaminated wounds. *J Am Coll Emer Phys* 3:375-381, 1974.
2. Brunius U, Akren Chr: Healing impairment of skin incisions closed with silk sutures. *Acta Chir Scand* 135:369-381, 1969.
3. Lewis JR, Jr: Facial scars resulting from vehicular accidents. *Clinics in Plastic Surgery* 2:143-166, 1975.
4. Forrester JC, Zederfeldt BH, Hayes TL, Hunt TK: Wolff's Law in relation to the healing wound. *J Trauma* 10:770-779, 1970.

3M COMPANY

UP-TO-DATE CUMULATIVE INDEX

Cancer

A Journal of the American Cancer Society, Inc.

TEN-YEAR CUMULATIVE INDEX OF SUBJECTS AND AUTHORS

VOLUMES 18–34. JANUARY 1965–DECEMBER 1974

The 10-year Cumulative Index to CANCER, printed in an easy-to-locate format is a convenient useful reference to the findings and developments in cancer as published in this official publication of The American Cancer Society during the years 1965 through 1974.

Completely cross-referenced, the key indexing words are those of the Medical Subjects Headings (MESH) of the National Library of Medicine.

In the Subject Index, under appropriate category headings set in bold face type, the complete title to each article is listed followed by author's name in parentheses, and the specific volume, page citation. Over 25,000 subject entries are included.

The Author Index, comprising some 10,000 entries, lists the principal author/s for each article and also cites volume and page location of the article.

In 328 pages, 7½ × 10¼, the outward appearance of the Cumulative Index matches that of the Journal CANCER itself. Price postpaid is $25.00 per copy. U.S., $26.00 all others.

CANCER

J. B. Lippincott Company
Attn. J. W. Bradley, Circulation Manager
East Washington Square, Philadelphia, Pa. 19105

Please send ______ copies of CANCER's Ten-Year Cumulative Index (1965–1974), at $25.00 per copy postpaid U.S. ($26.00 all others).

☐ Payment herewith ☐ Send Invoice

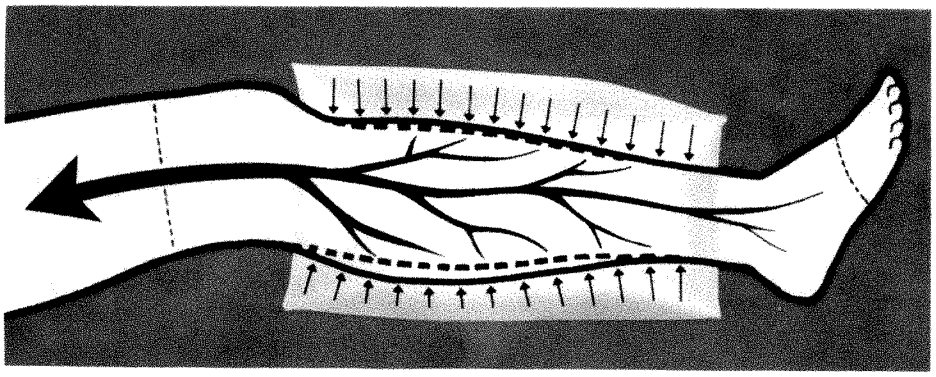
Name ____________________
(Please Print)

Address ____________________

City/State/Zip ____________________

Up to 100,000 deaths from Pulmonary Embolism can be prevented

Now you can ambulate your patients on the table with the Venodyne® intermittent compression system.



- ***Venodyne simulates calf muscle action.***
- ***Venodyne is totally non-invasive and non-pharmacologic.***
- ***Venodyne is simple to operate, compact, noiseless.***

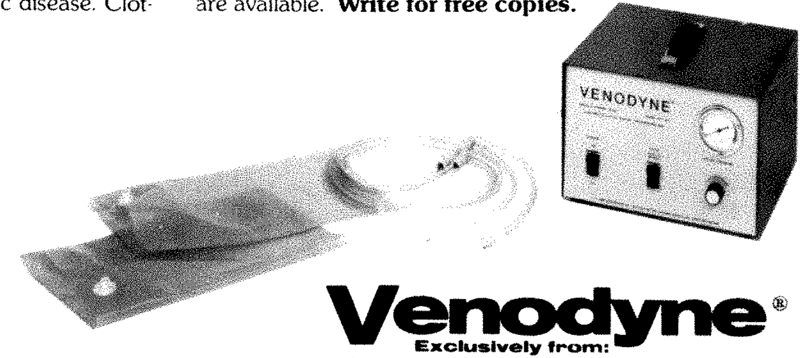
Annually about 6,000,000 adults in the United States suffer from episodes of pulmonary embolization and the mortality rate is close to 100,000 per year.[1] The deep leg veins are the source of the embolism in most patients.[2] And two-thirds of the deaths from massive embolism have been considered to be potentially preventable.[2] Additionally, it has been estimated that 50% or more of patients presenting with venous thrombosis suffer from some form of post-thrombotic syndrome by 5 to 10 years after the thrombotic event[2].

Early ambulation, leg exercises and elastic stockings have not significantly reduced the incidence of thrombophlebitic disease. Clotting normally commences before prophylactic measures have been instituted... usually while the patient is on the operating table. The various anticoagulants are the occasion of numerous contraindictions and complications.

Non-invasive, non-pharmacologic VENODYNE prophylaxis has been clinically shown to be as effective as anticoagulation, and much more effective than the various other physical methods of prophylaxis.

The VENODYNE system employs an inflatable plastic leg sleeve providing intermittent calf compression to simulate the normal calf muscle action of venous return. In essence, the system ambulates the patient on the operating table while under general anesthesia, or during any period of bed confinement. The system is safe, simple, and practical to use—and it's virtually trouble-free. Patient and nurse acceptance has been excellent.

Reprints of a number of professional papers on intermittent compression prophylaxis are available. **Write for free copies.**



Venodyne®

Exclusively from:

Lyne-Nicholson, Inc.
1000 Highland Ave., Needham Heights
MA 02194 Tel. 617-449-4900

1. *Cudkowicz and Sherry,* Heart and Lung, Vol 7, No 1, Jan-Feb 1978
2. *Gallus,* Venous Thromboembolism, Prevention and Treatment, Appleton-Century-Crofts, New York, NY 1976

Reliable and safe hemostat

to help control small-vessel bleeding without injuring vital tissue

SURGICEL

TRADEMARK

Absorbable Hemostat

(oxidized regenerated cellulose)

SURGICEL Absorbable Hemostat
TRADEMARK
(oxidized regenerated cellulose)

FOR SURGICAL USE

(For dental applications of this product, reference should be made to the package insert for dental use.)

DESCRIPTION: SURGICEL Absorbable Hemostat is a chemically-sterilized, absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and can be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance.

ACTIONS: The mechanism of action whereby SURGICEL accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors including the amount used, degree of saturation with blood, and the tissue bed.

INDICATIONS: SURGICEL Absorbable Hemostat (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective.

CONTRAINDICATIONS: Although packing or wadding sometimes is medically necessary, SURGICEL Absorbable Hemostat should not be used in this manner unless it is to be removed after hemostasis is achieved.

SURGICEL should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

When SURGICEL is used to help achieve hemostasis around the spinal cord in laminectomies, or around the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure.

SURGICEL should not be used to control hemorrhage from large arteries.

SURGICEL should not be used on *non-hemorrhagic serous oozing surfaces,* since body fluids other than whole blood, such as serum, do not react with SURGICEL to produce satisfactory hemostatic effect.

WARNINGS: SURGICEL Absorbable Hemostat is supplied sterile and should not be autoclaved because autoclaving causes physical breakdown of the product.

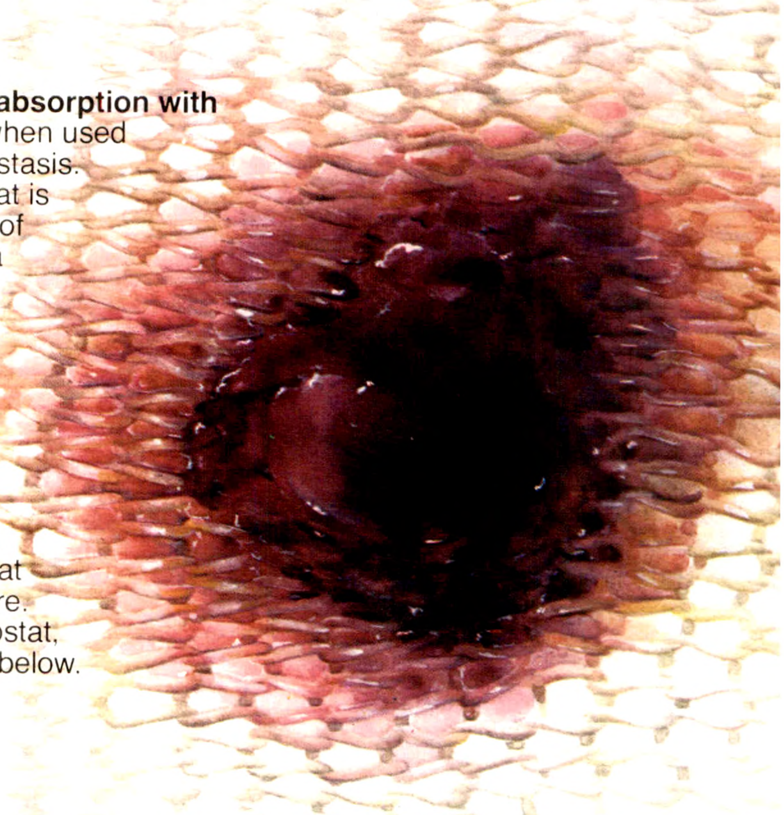
SURGICEL is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

Closing SURGICEL in a contaminated wound without drainage may lead to complications and should be avoided.

The hemostatic effect of SURGICEL is

©Johnson & Johnson 1975

Wide hemostatic application in surgery. SURGICEL* Absorbable Hemostat is a pliable knitted fabric that has been found to be inherently and dependably hemostatic when used as an aid in the control of small-vessel bleeding in abdominal, thoracic, neurosurgical, orthopedic, cardiovascular, gynecologic and otorhinolaryngologic procedures, in superficial open wounds and on donor sites. SURGICEL Absorbable Hemostat is a valuable adjunct in the control of small-vessel bleeding when ligation or other conventional methods of control are impractical or ineffective.



Rapid and complete absorption with virtually no tissue reaction when used properly in minimal amounts for hemostasis. SURGICEL Absorbable Hemostat is completely absorbable from sites of implantation after it has become a gelatinous mass that aids in the formation of a clot.

Convenient to use. SURGICEL Absorbable Hemostat requires no additional hemostatic preparation; it is ready for use directly from the vial. When exposed to blood, it adheres readily to tissues but generally not to dry instruments or dry surgical gloves. SURGICEL Absorbable Hemostat should be stored at controlled room temperature. Before using SURGICEL Absorbable Hemostat, please refer to product information below.

greater when it is applied dry; therefore it should not be moistened with water or saline.

SURGICEL should not be impregnated with *anti-infective* agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved. It *must* always be removed from the site of application after use in laminectomy procedures and from foramina in bone when hemostasis is obtained. This is because SURGICEL, by swelling, may cause nerve damage by pressure in a bony confine. Paralysis has been reported when used around the spinal cord, particularly in surgery for herniated intervertebral disc.

PRECAUTIONS: Use only as much SURGICEL Absorbable Hemostat as is necessary for hemostasis, holding it in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction.

SURGICEL should be applied loosely against the bleeding surface. Wadding or packing should be avoided, especially within rigid cavities, where swelling may interfere with normal function or possibly cause necrosis.

In *urological procedures,* minimal amounts of SURGICEL should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.

Since absorption of SURGICEL could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.

If SURGICEL is used temporarily to line the cavity of large open wounds, it should be placed so as not to overlap the skin edges. It should also be removed from open wounds by forceps or by irrigation with sterile water or saline solution after bleeding has stopped.

Precautions should be taken in *otorhinolaryngologic surgery* to assure that none of the material is aspirated by the patient. (Examples: controlling hemorrhage after tonsillectomy and controlling epistaxis.)

Care should be taken not to apply SURGICEL too tightly when it is used as a wrap during vascular surgery (see "ADVERSE REACTIONS" section).

ADVERSE REACTIONS: "Encapsulation" of fluid and foreign body reactions have been reported.

There have been two reports of stenotic effect when SURGICEL Absorbable Hemostat has been applied as a wrap during *vascular surgery.* Although it has not been established that the stenosis was directly related to the use of SURGICEL, it is important to be cautious and avoid applying the material tightly as a wrapping.

Possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy have been reported. There has been one report of a blocked ureter after kidney resection, in which postoperative catheterization was required.

Occasional reports of "burning" and "stinging" sensations and sneezing when SURGICEL has been used as packing in epistaxis, are believed due to the low pH of the product.

Burning has been reported when SURGICEL was applied after nasal polyp removal and after hemorrhoidectomy. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL was applied on surface wounds (varicose ulcerations, dermabrasions, and donor sites) also have been reported.

SURGIKOS

A Johnson & Johnson Company

New Brunswick, New Jersey 08903

---

*Trademark of Johnson & Johnson

Not All Postsurgical Patients Should Receive Potent Injectable Narcotics

CAUTION

In patients with decreased respiratory reserve, morphine and related narcotics must be used with great caution.

High Risk Patients

- Severely obese patients
- Patients with kyphoscoliosis
- Patients with chronic cor pulmonale
- Emphysematous patients
- Asthmatic patients

Many patients with such conditions are already utilizing compensatory mechanisms, such as increased respiratory rate. Many may have decreased sensitivity to elevated plasma CO_2 stimulation. The further imposition of the depressant effects of narcotics can be disastrous.

Consider

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of
pentazocine lactate injection, NF

Talwin shows infrequent occurrence of certain adverse effects* as:

- Respiratory depression (see below)
- Circulatory depression
- Shock
- Tachycardia
- Urinary retention

The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g. from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

There have been instances of psychological and physical dependence on Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. Patients with a history of drug dependence should be under close supervision while receiving Talwin. In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

For immediate pain control without many of the risks of narcotic analgesics:

Talwin®

30 mg. parenterally q. 3 to 4 hours.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

*See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of
pentazocine lactate injection, NF

Relieves pain of a moderate to severe nature.

Please consult full prescribing information before prescribing. A summary follows:
Talwin is intended for the relief of moderate to severe pain. 30 mg. is usually as effective an analgesic as morphine 10 mg. or meperidine 75 to 100 mg. The duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15 to 20 minutes after intramuscular or subcutaneous injection and within 2 to 3 minutes after intravenous injection. Talwin is a weak narcotic antagonist with sedative activity. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

CONTRAINDICATION

Hypersensitivity to pentazocine.

WARNINGS

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, animal studies have demonstrated that Talwin is tolerated less well subcutaneously than intramuscularly.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

PRECAUTIONS

The possibility that Talwin may cause respiratory depression should be considered. Talwin should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

ADVERSE REACTIONS

The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face, toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

Adults, Excluding Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg.

See Warnings in package insert as to recommended sites and routes of administration.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

OVERDOSAGE

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

HOW SUPPLIED

Uni-Amp®—Individual unit dose ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in boxes of 25.

Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in (nested) boxes of 25.

Each 1 ml. contains pentazocine lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing pentazocine lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

4004

The Role of Peritoneal Lavage in Severe Acute Pancreatitis

JOHN H. C. RANSON, M.D., FRANK C. SPENCER, M.D.

From the Department of Surgery, New York University Medical Center, New York, New York

Encouraged by reports of the therapeutic efficacy of peritoneal lavage in small series of five or six patients with acute pancreatitis, we have evaluated this treatment in 24 patients with "severe" pancreatitis. One hundred and three patients with "severe" pancreatitis (28% mortality) were separated from 347 with "mild" pancreatitis (0.9% mortality) by previously described early objective signs. Early treatment (Day 0–7) of "severe" pancreatitis included peritoneal lavage through catheters placed nonoperatively in 18 (Group A) and by catheters placed at laparotomy in six (Group C). Early treatment of nonlavaged patients with "severe" pancreatitis was by standard nonoperative measures in 61 (Group B) and included early operation in 18 (Group D). Lavage was continued for 48–96 hours, usually using 36–48 L/24 hours of balanced isotonic dialysate fluid, and was uncomplicated. Lavage led to striking immediate clinical improvement and no lavaged patient (Groups A and C) died during the first 10 days of treatment for pancreatitis. By contrast, 45% of deaths in nonlavaged patients (Groups B and D) occurred during this early period, usually from cardiovascular or respiratory failure. Although lavage reduced mortality in subgroups of patients, ultimate overall survival was not affected (Group A, 83%; B, 84%; C, 33%; D, 33%). Late peripancreatic abscesses caused most deaths in lavaged patients. These data show that peritoneal lavage is a highly effective adjunct to the treatment for early complications of severe acute pancreatitis and dramatically reduces early mortality. Lavage does not prevent the late local sequelae of peripancreatic necrosis.

PERITONEAL LAVAGE has been recommended in the management of severe acute pancreatitis on the basis of experimental studies[3,36–39] and clinical experience with small groups of patients.[6,13,14,45] Encouraged by these reports, we carried out a small controlled clinical trial which indicated that lavage was indeed associated with a striking reduction in the morbidity of severe acute pancreatitis.[32] The results of this trial have led to the wider application of peritoneal lavage in the early management of patients judged to have severe acute pancreatitis. The present report reviews our overall experience with the clinical management of acute pancreatitis and further evaluates the therapeutic efficacy of peritoneal lavage.

Materials and Methods

Patient Population

A total of 450 consecutive patients were treated for acute pancreatitis on the surgical services at Bellevue Hospital and New York University Medical Center between January 1971 and May of 1977. There were 99 women and 351 men. Their age ranged from 19 to 92 years with a mean age of 44 years. The etiological associations and history of previous episodes of pancreatitis are shown in Table 1. Seventy per cent gave a history of prolonged alcohol abuse and 16% had documented cholelithiasis. The diagnosis of pancreatitis was demonstrated by operation or autopsy in 94, and in 356 it was made on the basis of abdominal pain and tenderness with vomiting, serum amylase levels above 200 Somogyi units per cent and an overall clinical course compatible with acute pancreatitis. Patients in whom elevated serum amylase levels were recorded after operation or with biliary tract disease but in whom no other clinical or operative evidence of pancreatitis was noted are not included. Patients with pancreatitis following pancreatic trauma or direct surgical procedures on the pancreas were not studied.

Severity of Pancreatitis.

The risk of death or major complications in individual patients was estimated by a previously described system of early objective prognostic signs.[30–32] The signs are listed in Table 2. The change in hematocrit and in blood urea nitrogen levels represent the overall change from the initial value to the 48 hour value. Fluid sequestration was estimated by subtracting the total volume of nasogastric aspirate, urinary output and any other drainage from the volume of fluids administered intravenously during the initial 48 hour period. No attempt was made to estimate insensible fluid loss and fluid retained during the initial 24 hours but excreted during the second 24 hours is not reflected in the total.

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests: John H. C. Ranson, M.D., Department of Surgery, New York University Medical Center, 560 First Avenue, New York, New York 10016.

0003-4932-78-0500-0565-0115 © J. B. Lippincott Company

TABLE 1. *Sex, Etiologic Associations, History of Previous Episodes of Pancreatitis and Mortality in All Patients**

		Patients with <3 Positive Signs			Patients with ≥3 Positive Signs		
	Total Number	Number	No. Dead	Per cent Dead	Number	No. Dead	Per cent Dead
All Patients	450	347	3	0.9	103	29	28
Etiology:							
Alcohol	315	260	2	0.8	55	10	18
Biliary	74	53	1	1.9	21	4	19
Postoperative	23	7	0	0	16	10	63
Other	38	27	0	0	11	5	45
Previous Episodes:							
0	282	200	2	1.0	82	25	30
1	76	60	0	0	16	4	25
>1	92	87	1	1.1	5	0	0
Men	351	279	2	0.7	72	20	28
Women	99	68	1	1.5	31	9	29

* Patients with less than three positive prognostic signs and those with three or more positive prognostic signs.

The only measurements which have been deliberately excluded from prognostic consideration are blood glucose levels in patients with known pre-existing diabetes mellitus.

Each of the early prognostic signs has been shown by statistical analysis to be related to overall morbidity in our population of patients with pancreatitis[30,31] and, as shown in Figure 1, the probability of death or major complication is related to the number of positive early signs recorded.

In the present study, 347 patients had less than three positive prognostic signs and are designated as having had "mild" pancreatitis. Three of these patients (0.9%) died; one from respiratory complications following cholecystectomy; one from an apparent pulmonary embolus following a late abdominal drainage procedure and one vomited, aspirated and suffered cardiac arrest in the admitting area. Although initially resuscitated, he did not survive. Ten additional patients (2.9%) in this group required more than seven days of intensive care. Patients with less than three positive prognostic signs will not be considered further in this report.

TABLE 2. *The Eleven Early Objective Signs Used to Classify the Severity of Pancreatitis*

At Admission or Diagnosis
- Age over 55 years
- White blood cell count over 16,000/cu. mm.
- Blood glucose over 200 mgm %
- Serum lactic dehydrogenase over 350 I.U./liter
- Serum glutamic oxaloacetic transaminase over 250 Sigma Frankel Units %

During Initial 48 Hours
- Hematocrit fall greater than 10 percentage points
- Blood urea nitrogen rise more than 5 mg %
- Serum calcium level below 8 mgm %
- Arterial P_{O_2} below 60 mm Hg
- Base deficit greater than 4 meq/liter
- Estimated fluid sequestration more than 6000 ml

One hundred and three patients had three or more positive prognostic signs and were designated as having "severe" pancreatitis. They included 31 women and 72 men. The etiologic associations and history of previous documented episodes of acute pancreatitis are shown in Table 1. The diagnosis was demonstrated by operation or autopsy in 45 (44%) of these patients.

Treatment of Pancreatitis

All patients were managed with nasogastric suction, intravenous fluids and antibiotics, usually Ampicillin 2G intravenously every six hours. In most patients, nasogastric suction was maintained until all evidence of pancreatic inflammation had resolved before cautiously resuming a low fat oral diet. An indwelling urethral

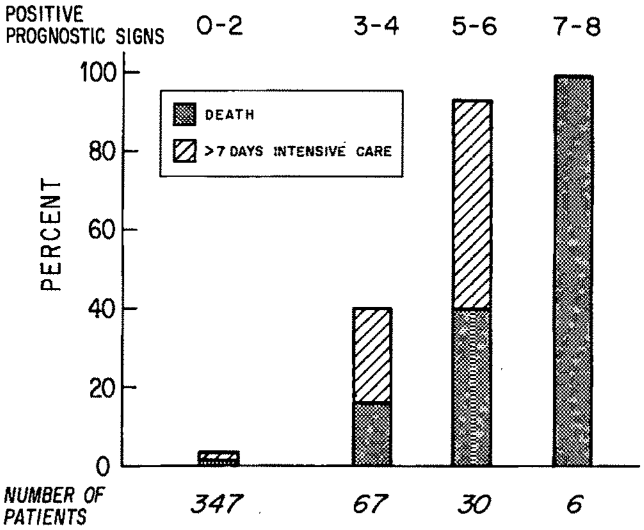


FIG. 1. The relationship between the number of positive early prognostic signs recorded and the per cent mortality and morbidity, as reflected by the need for more than seven days of treatment in an intensive care unit.

TABLE 3. *Overall Mortality of Patients with Three or More Positive Prognostic Signs Related to Treatment during the Initial Seven Days after Diagnosis**

	All Patients		Alcohol		Etiologic Subgroups					
					Biliary		Postoperative		Other	
Early treatment groups	No.	% Dead	No.	% Dead	No.	% Dead	No.	% Dead	No.	% Dead
Nonoperative lavage (A)	18	16.7	14	21	2	0	1	0	1	0
Nonoperative only (B)	61	16.4	34	9	10	0	9	44	8	38
Operative lavage (C)	6	66.7	2	50	1	0	2	100	1	100
Other operations (D)	18	66.7	5	60	8	50	4	100	1	100

* The relationship of etiologic associations to mortality in the different early treatment groups is also shown.

catheter was introduced to allow close monitoring of urinary output and a central venous catheter was usually placed. Oxygen was administered by face mask to many patients and 27 (26%) patients with "severe" pancreatitis required endotracheal intubation and mechanically assisted ventilation.

Additional treatment during the first seven days after diagnosis of "severe" pancreatitis was grouped into four categories. Group A, which included 18 patients, underwent non-operative peritoneal lavage. Group B was 61 patients who were managed non-operatively without peritoneal lavage. Group C was six patients who underwent early laparotomy for diagnosis. Once the diagnosis was established, peritoneal lavage catheters were introduced and the abdomen was closed. No pancreatic drains were placed and no other operative procedures were carried out except for cholecystostomy construction in two patients with suspected biliary disease. Group D was 18 patients who underwent early operative procedures which were usually more extensive than those in Group C. The operative procedures were: partial pancreatic resection in five, wide pancreatic sump drainage with cholecystostomy, gastrostomy and jejunostomy in five; cholecystectomy with or without common bile duct exploration in five; cholecystostomy alone in one and local lesser sac drainage in two. Postoperative irrigation of pancreatic sump drains was carried out in five group D patients,[31] but none received formal general peritoneal lavage. The etiologic associations of the patients in the four treatment groups are shown in Table 3.

In Group A, peritoneal lavage catheters were introduced under local infiltration anesthesia, usually by a 4–5 cm incision in the midline below the umbilicus with direct visualization of the peritoneum. The fascia, subcutaneous tissues and skin were closed about the catheter. In all lavaged patients, (Groups A and C), the fluid used was an approximately isotonic balanced electrolyte solution containing 15 g per liter of dextrose (Dianeal®). Eight milliequivalents of potassium, 1000 USP units of heparin and 250 mg of ampicillin were added to each two liters of fluid. Hypertonic fluid with 42.5 g of dextrose per liter was used for part of the lavage period in several patients. In general, two liters of lavage fluid were run into the peritoneal cavity under gravity. It was left intraperitoneally for approximately 30 minutes and then drained out by gravity. This cycle was usually repeated hourly. Some patients required smaller volumes of fluid and a shorter cycle because of exacerbation of respiratory distress by increased abdominal distension. Lavage was instituted within 48 hours of diagnosis in all patients and continued for periods of 48–96 hours depending on the patient's clinical response.

In the first nine patients treated with nonoperative peritoneal lavage (Group A), as in most other patients, oral diet intake was resumed after clinical signs of pancreatic inflammation had resolved. In the last nine patients in this Group, nasogastric suction was usually maintained for a minimum of 14 days, even if the pancreatitis appeared clinically resolved. The nutritional status of patients who were without oral intake for prolonged periods was supported with intravenous hyperalimentation or jejunal feedings.

Results

Twenty-nine of 103 patients (28%) with "severe" acute pancreatitis died. Death was associated with intra-abdominal sepsis in 20. It was due to cardiovascular failure in six, respiratory failure in two and a cerebrovascular accident in one.

Overall survival was 83% in those treated with early non-operative peritoneal lavage (Group A) compared to 84% in those treated by conventional nonoperative measures (Group B) (Table 3). However, as shown in Figure 2, there were a large number of Group B patients with only moderately "severe" pancreatitis. There were no deaths in seven Group A patients with three or four positive signs compared to six deaths (12%) in 49 similar Group B patients.

Among those who underwent laparotomy during the

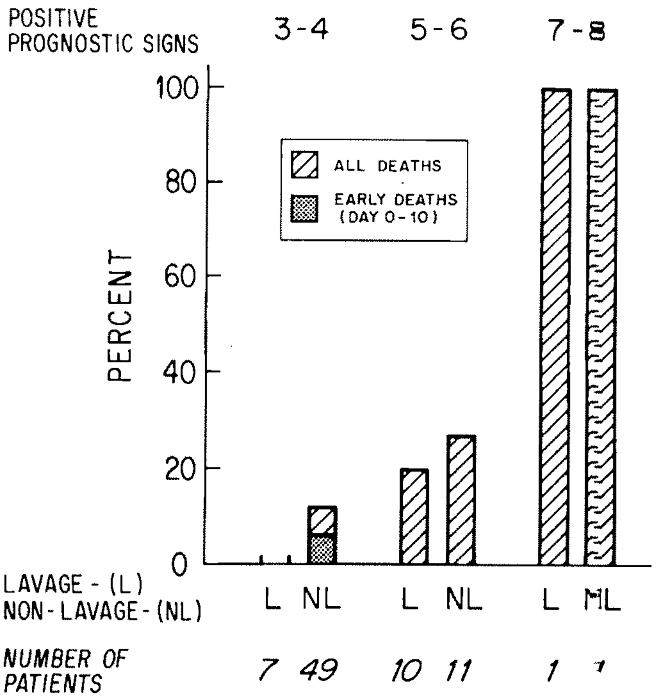


FIG. 2. The influence of peritoneal lavage on early mortality (days 0–10) and overall mortality in patients with three or more positive prognostic signs who did not undergo laparotomy during the initial seven days of treatment.

first seven days of treatment (Groups C and D), the operative procedure was limited to placement of lavage catheters and possible cholecystostomy in only six patients. In this lavaged group (Group C) overall mortality was 67% and was equal to that in those who underwent other early surgical procedures (Group D) (Fig. 3).

Although overall survival rates were not greatly improved by lavage, the time of death was dramatically altered. As shown in Figures 2 and 3, no lavaged patient died during the first ten days of treatment for pancreatitis while ten of 22 (45%) nonlavaged deaths occurred during this early period. In nonlavaged patients, cardiovascular or respiratory failure without intra-abdominal sepsis caused seven of 22 deaths (32%). Only one of seven deaths (14%) in lavaged patients was from these causes. This was in a patient who required emergency gastrectomy on the tenth hospital day for massive gastric bleeding. Postoperatively, fulminating respiratory insufficiency developed which led to death on the fourteenth day. All other deaths in lavaged patients were related to peripancreatic abscesses.

The possibility that peritoneal lavage was associated with an increase in the frequency of late peripancreatic abscesses was evaluated. Excluding the nine patients who died without developing intra-abdominal sepsis, abscesses occurred in three of 17 (18%) Group A patients, 11 of 58 Group B patients (19%), four of six (67%) Group C patients and nine of 13 (69%) Group D patients. The relationship between the number of early positive prognostic signs, early management and late abscesses is shown in Figure 4.

Three of the first nine patients in Group A (nonoperative lavage) died. Review of the management of these patients showed that, as with most other patients, oral diet had been resumed when clinical and biochemical evidence of pancreatitis had resolved. In two patients, each with five positive prognostic signs, there was a dramatic resolution of clinical signs of pancreatitis during lavage, which led to the resumption of oral diet on the seventh and eighth day of treatment, respectively. The mean period without oral feedings in patients with five or six positive signs was 21.5 days, and early oral feedings in these two lavaged patients was followed by prompt and dramatic evidence of reactivation of pancreatitis with eventual death. In the last nine patients in Group A, nasogastric suction was therefore usually maintained for an arbitrary minimum period of 14 days. As a result, the mean period without oral feedings rose from 15 days in the first nine Group A patients to 25 days in the second nine patients. However, none of the last nine Group A patients died.

The overall relationship between the duration of

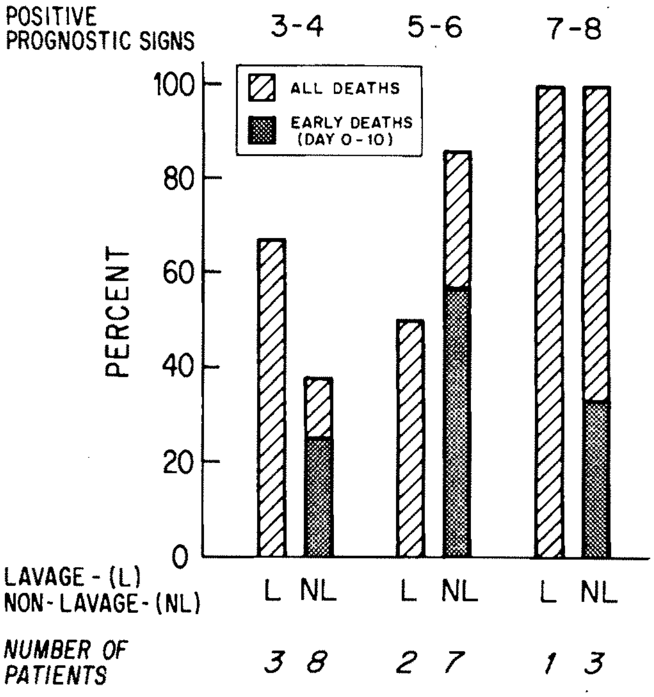


FIG. 3. Early mortality (days 0–10) and overall mortality in patients with three or more positive prognostic signs who underwent laparotomy during the initial seven days of treatment. Lavage operations were limited to placement of lavage catheters with cholecystostomy in two patients. Nonlavage operations are listed in the text.

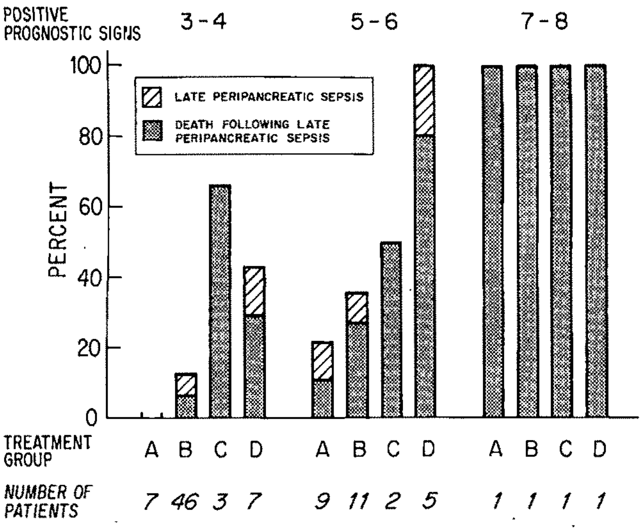


FIG. 4. The frequency of peripancreatic sepsis and death following peripancreatic sepsis related to positive prognostic signs and to early treatment group. (Group A—non-operative lavage, Group B—conventional nonoperative, Group C—lavage operation and Group D—other operations.) Nine patients who died without peripancreatic sepsis are excluded.

nasogastric suction and mortality in patients in Groups A and B is shown in Table 4. This analysis excludes three patients who died within the first eleven days of treatment. As expected, the period without oral intake was usually greater in patients with more severe pancreatitis and a greater risk of death as estimated by prognostic signs. Nonetheless, the mortality was lower in patients kept without oral feeding for more than 11 days than it was in those in whom oral diet was resumed earlier. In five of the six patients who died after receiving oral feedings within the first 11 days of treatment, death resulted from pancreatic abscesses.

Discussion

Although most patients with acute pancreatitis recover following conventional treatment with nasogastric suction, intravenous fluid administration and general supportive care, five to 26% develop serious or lethal complications.[1,7,16,25,27,29,44,48] Improved methods of management are required and frequently proposed for this latter group of patients. Evaluation of proposed treatments has, however, been hampered by several factors which include difficulty in determining the presence of acute pancreatitis, its widely diverse etiologic associations, a multiplicity of life-threatening complications and marked variability of natural history.

The unquestionable presence of acute pancreatitis can be demonstrated only by laparotomy or autopsy.[5,49] These criteria were met by only 94 patients or 21% of this overall series and 45 or 44% of those with "severe" pancreatitis. Unfortunately such strict criteria would certainly exclude many patients with pancreatitis and they clearly would not permit evaluation of non-operative treatment of the disease. In the present study, we have attempted to be as accurate as possible about diagnosis. Nonetheless, as in other clinical studies, it is possible that some patients, such as those with severe uncomplicated alcoholic gastritis, may have been mistakenly included. Similarly, patients who recovered uneventfully from pancreatitis occurring postoperatively or with biliary disease may have been overlooked.

Acute pancreatitis occurs most commonly in patients with gallstones or chronic alcoholism.[16,44] Many other etiologic associations have, however, been described, including such diverse factors as pregnancy[50] or cardiac surgery.[9] Patients with each of these associations are included in the present study and, although the course of illness may be markedly influenced by its underlying cause, many of the clinical manifestations and complications of acute pancreatitis appear to follow common patterns regardless of basic etiology.[32,34,35]

The possible life-threatening manifestations of pancreatitis of any etiology are multiple and include electrolytic disturbances, gastrointestinal bleeding, hyperglycemia, colonic necrosis and renal failure.[18,22,25,28,29,41] It is probable that a treatment which was effective in limiting the severity of pancreatic inflammation itself would reduce the morbidity of all complications. Until such a treatment is available, management of patients with pancreatitis requires attention to several different areas and the possibility that a treatment is effective in reducing morbidity from one complication, but not from others, should not be overlooked. For purposes of analysis, the most common major causes of death in acute pancreatitis may be classified as cardiovascular failure, respiratory failure and intra-abdominal sepsis, although sharp distinctions are not always possible. Renal failure has been a significant

TABLE 4. *Mean Period without Oral Feedings Related to Positive Early Prognostic Signs**

Positive Early Prognostic Signs	3–4	5–6	7–8	3–8
Number of patients	53	21	2	76
Mean NPO days	12.1	21.5	12.0	14.7
Patients NPO < 11 days				
Number	35	4	1	40
Per cent dead	9	50	100	15
Patients NPO ≥ 11 days				
Number	18	17	1	36
Per cent dead	0	18	100	11

* The mortality in patients who received oral feedings during the initial 11 days of treatment compared to that in patients who did not is also shown. This table includes only those patients whose initial management was non-operative (Groups A and B) and excludes three patients who died during the initial 11 days of treatment.

cause of death in some reports,[16,29] but in the present series frank renal failure requiring hemodialysis occurred in only two patients, both of whom had massive intra-abdominal sepsis.

In Fitz's classic description of acute pancreatitis in 1889,[10] approximately two-thirds of deaths occurred with "collapse," usually during the first few days of illness. About one-third of deaths occurred after weeks or months from "exhaustion," with pancreatic suppuration. At the time of Fitz's report, few measures were available for the treatment of early cardiovascular and respiratory failure and continued pancreatic stimulation by oral feedings may have contributed to late pancreatic abscesses in patients with milder pancreatitis.[34] However, in studies published during the last 15 years, the pattern has been remarkably similar. Death has been attributed to "shock," pneumonia or respiratory failure in 66–80% of patients[11,16,22,27,44] and most such deaths have occurred in the first 14 days of treatment.[8,43,44] Death was due to peripancreatic sepsis in 14–35% of cases[8,16,22,44] and these deaths usually occurred after the first two weeks of treatment.[8,34,44]

In the present overall group of 450 patients, death was primarily due to cardiovascular or respiratory failure in nine of 31 patients (29%) and a cerebrovascular accident in one (3%). These deaths occurred on days one to 16 (median day 5). Twenty-one deaths (68%) were associated with intra-abdominal sepsis and occurred on days eight to 131 (median day 23). It is possible that the relatively low proportion of early deaths and high proportion of late deaths in this series reflects poor prevention and management of late peripancreatic sepsis. Since, however, the overall mortality of 6.5% was not higher than that in other recent series,[7,16,48] it is probable that current improvements in monitoring and support of cardiovascular and respiratory failure have been effective in reducing deaths from these causes.

Perhaps the most serious obstacle to the evaluation of treatment of acute pancreatitis has been the marked variation in severity of disease. Since most patients recover with conventional treatment and since the early identification of "severe" pancreatitis has usually included subjective criteria, it has often been possible that reported clinical results reflect the severity of disease being treated rather than the efficacy of treatment. In order to develop an objective method for the early identification of patients with severe pancreatitis, a statistical analysis was carried out of 43 measurements made during the initial 48 hours of treatment in the first 100 patients in this series.[31] From this analysis, the eleven early prognostic signs recorded in Table 1 were identified. Each sign correlated with subsequent overall morbidity and mortality and, as shown in Figure 1, the risk of death or major morbidity is related to the number of positive early signs present. Many of the signs are nonspecific and not every patient with three, four or even five positive early signs was seriously ill. Nonetheless, the signs do provide an objective *method for* estimating the risk of major complications or death in groups of patients.[30–32,34] In the present study, they have been used to separate those with "mild" pancreatitis (<3 signs) and a 0.9% mortality from those with "severe" pancreatitis (≥3 signs) and a 28% mortality. In addition, those with "severe" pancreatitis have been subdivided into three groups: 67 patients with three or four positive signs and a 16% mortality; 30 patients with five or six positive signs and a 40% mortality; and six patients with seven or eight positive signs and a 100% mortality (Figs. 1–3).

General Management of "Severe" Acute Pancreatitis

Since, at present, there is no single measure which has been proved to limit pancreatic inflammation, the treatment of patients with "severe" pancreatitis remains multifaceted and must be individualized. Most patients are initially hypovolemic and careful monitoring and maintenance of intravascular volume is essential in all patients. Urinary output and renal function should be closely monitored.

Respiratory complications are a well-recognized feature of acute pancreatitis.[35] The frequent occurrence of early clinically occult respiratory insufficiency has recently been documented and necessitates regular arterial blood gas measurements in all patients with pancreatitis.[21,33,35] Patients with progressive respiratory insufficiency may benefit from restriction of intravenous fluids and administration of diuretics.[32,35] Severe respiratory failure requires endotracheal intubation and mechanically assisted ventilation with positive end-expiratory pressure. In this series, such assistance was provided to 27 patients (26%) with "severe" pancreatitis.

All patients in the present series were treated with nasogastric suction. It was intended that nasogastric suction would not only prevent vomiting and minimize abdominal distension, but also reduce pancreatic stimulation.[24,46] As previously reported,[32,34] it has appeared that premature discontinuation of gastric suction and resumption of oral feedings is frequently followed by reactivation of pancreatitis and further complications, especially pancreatic abscess formation. At present, we attempt to maintain nasogastric suction until all evidence of pancreatitis has resolved and the mean period without oral intake is 15 days in patients with three or more positive signs. The therapeutic value of nasogastric suction has recently been questioned on the basis of a small controlled trial in patients with mild alcoholic pancreatitis.[23] However, in that trial, nasogastric suction was associated with 22 and 17% reductions in the mean duration of abdominal pain and fever respectively. Table 4 shows the relationship between the period without oral feedings and mortality in the present series of patients with "severe" pancreatitis. Although this period tended to be longer in patients with more positive prognostic signs and therefore higher risks of complications, those who received oral feedings during the first 11 days of treatment had a higher overall mortality than did those who were not fed during this time.

The role of abdominal operation early in the course of severe acute pancreatitis has been controversial. Our early studies[31,32,34,35] have led us to believe that early laparotomy is associated with significantly increased morbidity in acute pancreatitis, primarily from respiratory complications and late peripancreatic abscesses. The results of the present review (Figs. 2 and 3) support these earlier findings and, furthermore, as shown in Table 3, early laparotomy did not appear to benefit any etiologic subgroup. Nonetheless, the accurate differentiation of pancreatitis from mesenteric infarction, gangrenous cholecystitis or other conditions requiring urgent surgical correction necessitates laparotomy in some patients. At present, when pancreatitis is found at operation, the procedure is limited to placement of catheters for postoperative lavage and cholecystostomy in patients with associated cholelithiasis. Only six patients with three or more positive prognostic signs have been treated in this way and, thus far, overall mortality has been the same as that in patients undergoing more extensive procedures (Fig. 3).

Peritoneal Lavage

Peritoneal lavage for acute pancreatitis was initially reported by Wall in 1965.[45] He instituted peritoneal dialysis for renal failure occurring in three patients with severe acute pancreatitis and noted a dramatic improvement in their general clinical condition with ultimate survival in two patients. Subsequently, the treatment of pancreatitis by peritoneal lavage has been described in 21 patients, 11 of whom survived.[6,12–14,16] The timing and technique of lavage have varied and the severity of pancreatitis treated is not always clear; however, all reports have observed a marked immediate clinical improvement. Encouraged by these reports, we undertook a small controlled trial of peritoneal lavage in ten patients with "severe" acute pancreatitis. As previously reported,[32] the clinical improvement associated with lavage was striking and was reflected in a reduced period of intensive care and of hospitalization. The mean periods of leucocytosis, hyperamylasemia and hypocalcemia were also reduced in lavaged patients. The present review includes the five patients treated with non-operative peritoneal lavage as part of the controlled trial. In our subsequent experience, the rapid clinical improvement during peritoneal lavage has remained striking in most patients. The early value of lavage is further supported by the fact that no lavaged patient died during the first ten days of treatment for pancreatitis while 45% of deaths of nonlavaged patients occurred during this early period, usually from cardiovascular or respiratory failure.

The direct hazards of peritoneal lavage include injury to viscera by the catheter, increased respiratory distress due to abdominal distension by lavage fluid, hyperglycemia, and fluid overload if the lavage fluid is not returned from the peritoneal cavity. At present, lavage catheters are introduced through the peritoneum under direct vision and no visceral injury has been noted using this technique. Respiratory function is often impaired in patients with severe pancreatitis[33,35] and must be closely monitored during lavage. In some patients it has been necessary to use a smaller volume of lavage fluid and a shorter cycle to avoid undue respiratory distress. The tonicity of lavage fluid is maintained with glucose, and since glucose intolerance is common in severe pancreatitis, blood glucose levels must be closely monitored. In most patients the volume of peritoneal effluent has exceeded that of the lavage fluid by about 1000 ml per day. The tendency to a net fluid loss by the patient during lavage may be increased by using hypertonic lavage fluid and fluid overload should not be a problem if lavage volumes are closely monitored. Hypothermia and albumin loss in the lavage fluid are theoretical hazards which have not been significant problems in practice.

Three of our initial nine patients treated with non-operative peritoneal lavage died from late complications. One had seven positive early prognostic signs and died with massive peripancreatic sepsis. Two patients, however, had only five positive early signs. Each had a dramatic early response to lavage with apparent resolution of pancreatitis. Oral feedings were resumed early and were followed by prompt and severe recrudescence of pancreatitis and eventual death. It appeared that peritoneal lavage may have contributed to these deaths by producing resolution of clinical findings before the pancreatitis had completely subsided. It is, therefore, now our recommendation that nasogastric suction be maintained for an arbitrary minimum of 14 days in lavaged patients. Nutrition is supported during this period with intravenous alimentation. This policy has increased the mean duration of nasogastric suction in the last nine patients treated with non-operative lavage but there have been no deaths in this group. The possibility that lavage was producing an increase in the frequency of later peripancreatic abscesses was considered, but, as shown in Table 4, this was not the case.

Studies of peritoneal lavage in experimental acute pancreatitis in dogs[3,36,37,39] and in guinea pigs[38] have shown that lavage is associated with immediate general clinical improvement and decreased mortality. Lavage has also been reported to reduce the amount of fat necrosis[36,39] and pancreatic necrosis.[3,36]

The therapeutic efficacy of peritoneal lavage has generally been attributed to the removal of toxic materials in the peritoneal exudate in acute pancreatitis.[3,39,45] Since hemodialysis was not associated with a significant improvement in survival from severe acute pancreatitis,[4] it is not probable that the efficacy of lavage is due to improvement of fluid and electrolyte balance or to removal of dialysable substances from the blood. Studies of the peritoneal exudate found during acute pancreatitis have shown that this exudate contains amylase, lipase, phospholipase A, trypsinogen, proteolytic proenzyme, prostoglandin-like activity and kinin-forming enzymes.[15,17,19,20,37,40,42,47] Furthermore, the exudate has been shown to produce systemic hypotension,[2,20,40] histamine release[26] and increased vascular permeability.[42] Whatever the factor or factors which are responsible for the toxic effect of the peritoneal exudate in acute pancreatitis, it is clear that its removal, however incomplete, by peritoneal lavage is associated with a decreased early mortality from severe acute pancreatitis.

Conclusions

Previously reported prognostic signs provide an objective estimate within 48 hours after diagnosis of the risk of death from acute pancreatitis. The signs permit the early identification of those patients who may require special therapeutic measures and also allow evaluation of the efficacy of therapy in groups of patients.

Peritoneal lavage appears to be a safe and effective adjunct to the early treatment of severe acute pancreatitis and has prevented all deaths during the first ten days of treatment. Although early lavage has increased total survival in subgroups of patients, overall improvement in mortality has been disappointing due to a failure to prevent the occurrence and morbidity of late peripancreatic sepsis. Better methods are still needed to limit and to treat the local sequellae of severe peripancreatic necrosis.

References

1. Albo, R., Silen, W. and Goldman, L.: A Critical Clinical Analysis of Acute Pancreatitis. Arch. Surg., 86:1032, 1963.
2. Amundsen, E., Ofstad, E. and Hagen, P-O.: Experimental Acute Pancreatitis in Dogs. I. Hypotensive Effect Induced by Pancreatic Exudate. Scand. J. Gastroenterol., 3:659, 1968.
3. Ancarani, E., Tersigni, R. and Vincenti, R.: Peritoneal Dialysis in the Treatment of Experimental Acute Pancreatitis. Bull. Soc. Int. Chir., 31:142, 1972.
4. Balsløv, J. T., Jørgensen, H. E. and Nielsen, R.: Acute Renal Failure complicating Severe Acute Pancreatitis. Acta Chir. Scand., 124:348, 1962.
5. Bernard, H. R., Criscione, J. R. and Moyer, C. A.: The Pathologic Significance of the Serum Amylase Concentration. Arch. Surg., 79:311, 1959.
6. Bolooki, H. and Gliedman, M. L.: Peritoneal Dialysis in Treatment of Acute Pancreatitis. Surgery, 64:466, 1968.
7. Cogbill, C. L. and Song, K. T.: Acute Pancreatitis. Arch. Surg., 100:673, 1970.
8. Enquist, I. F. and Gliedman, M. L.: Gross Autopsy Findings in Cases of Fatal Acute Pancreatitis. Arch. Surg., 77:985, 1958.
9. Feiner, H.: Pancreatitis after Cardiac Surgery. Am. J. Surg., 131:684, 1976.
10. Fitz, R. H.: Acute Pancreatitis. Boston Med. Surg. J., 70:181; and 205, 1887.
11. Foster, P. D. and Ziffren, S. E.: Severe Acute Pancreatitis. Arch. Surg., 85:252, 1962.
12. Freidell, H. V.: Pancreatitis and Renal Insufficiency. Am. J. Gastroenterol., 34:487, 1960.
13. Gjessing, J.: Peritoneal Dialysis in Severe Acute Hemorrhagic Pancreatitis. Acta Chir, Scand., 133:645, 1967.
14. Geokas, M. C., Olsen, H., Barbour, B. and Rinderknecht, H.: Peritoneal Lavage in the Treatment of Acute Hemorrhagic Pancreatitis. Gastroenterology, 58:950, 1970.
15. Gjone, E., Ofstad, E., Marton, P. F. and Amundsen, E.: Phospholipase Activity in Pancreatic Exudate in Experimental Acute Pancreatitis. Scand. J. Gastroenterol., 2:181, 1967.
16. Gliedman, M. L., Bolooki, H. and Rosen, R. G.: Acute Pancreatitis. Curr. Probl. Surg., (August), 1970.
17. Glazer, G. and Bennett, A.: Elevation of Prostaglandin-like Activity in the Blood and Peritoneal Exudate of Dogs with Acute Pancreatitis. Br. J. Surg., 61:922, 1974.
18. Hagen, P-O., Ofstad, E. and Amundsen, E.: Experimental Acute Pancreatitis in dogs. III. The Nature of the Phospholipase Activity of Pancreatic Exudate. Scand. J. Gastroenterol., 4:81, 1969.
19. Hagen, P-O., Ofstad, E. and Amundsen, E.: Experimental Acute pancreatitis in Dogs. IV. The Relationship between Phospholipase A and the Histamine-Releasing and Hypotensive Effects of Pancreatic Exudate. Scand. J. Gastroenterol., 4:89, 1969.
20. Huttunen, R.: The Proteolytic Proenzymes in the Peritoneal Exudate during Acute Experimental Pancreatitis of the Rat. Acta. Chir. Scand., 141:285, 1975.
21. Imrie, C. W. and Blumgart, L. H.: Acute Pancreatitis: A Prospective Study on Some Factors in Mortality. Bull. Soc. Int. Chir., 6:601, 1975.
22. Kune, G. A.: The Challenge of Severe Acute Pancreatitis. Med. J. Aust., 2:8, 1968.
23. Levant, J. A., Secrist, D. M., Resin, H., et al.: Nasogastric Suction in the Treatment of Alcoholic Pancreatitis. JAMA, 229:51, 1974.
24. Lium, R. and Maddock, S.: Etiology of Acute Pancreatitis; an Experimental Study. Surgery, 24:593, 1948.
25. Lukash, W. M.: Complications of Acute Pancreatitis. Arch. Surg., 94:848, 1967.
26. Ofstad, E., Amundsen, E. and Hagen, P-O.: Experimental Acute Pancreatitis in Dogs. II. Histamine Release Induced by Pancreatic Exudate. Scand. J. Gastroenterol., 4:45, 1969.
27. Olsen, H.: Pancreatitis. Am. J. Dig. Dis., 19:1077, 1974.
28. Paxton, J. R., and Payne, J. H.: Acute Pancreatitis. Surg. Gynecol. Obstet., 86:69, 1948.
29. Pollock, A. V.: Acute Pancreatitis. Br. Med. J., 1:6, 1959.
30. Ranson, J. H. C. and Pasternack, B. S.: Statistical Methods for

Quantifying the Severity of Clinical Acute Pancreatitis. J. Surg. Res., 22:79, 1977.

31. Ranson, J. H. C., Rifkind, K. M., Roses, D. F., et al.: Prognostic Signs and the Role of Operative Management in Acute Pancreatitis. Surg. Gynecol. Obstet., 139:69, 1974.
32. Ranson, J. H. C., Rifkind, K. M. and Turner, J. W.: Prognostic Signs and Non-operative Peritoneal Lavage in Acute Pancreatitis. Surg. Gynecol. Obstet., 143:206, 1976.
33. Ranson, J. H. C., Roses, D. F. and Fink, S. D.: Early Respiratory Insufficiency in Acute Pancreatitis. Ann. Surg., 178:75, 1973.
34. Ranson, J. H. C. and Spencer, F. C.: Prevention, Diagnosis and Treatment of Pancreatic Abscess. Surgery, 82:99, 1977.
35. Ranson, J. H. C., Turner, J. W., Roses, D. F., et al.: Respiratory Complications in Acute Pancreatitis. Ann. Surg., 179:557, 1974.
36. Rasmussen, B. L.: Hypothermic Peritoneal Dialysis in the Treatment of Acute Experimental Hemorrhagic Pancreatitis. Am. J. Surg., 114:716, 1967.
37. Rogers, R. E., and Carey, L. C.: Peritoneal Lavage in Experimental Pancreatitis in Dogs. Am. J. Surg., 111:792, 1966.
38. Rosato, E. F., Chu, W. H., Mullen, J. L. and Rosato, F. E.: Peritoneal Lavage Treatment of Experimental Pancreatitis. J. Surg. Res., 12:138, 1972.
39. Rosato, E. F., Mullis, W. F. and Rosato, F. E.: Peritoneal Lavage Therapy in Hemorrhagic Pancreatitis. Surgery, 74: 106, 1973.
40. Satake, K., Rozmanith, J. S., Appert, H. E., et al.: Hypotension and Release of Kinin-Forming Enzyme into Ascitic Fluid Exudate during Experimental Pancreatitis in Dogs. Ann. Surg., 177:497, 1973.
41. Shader, A. E. and Paxton, J. R.: Fatal Pancreatitis. Am. J. Surg., 111:369, 1966.
42. Takada, Y., Appert, H. E. and Howard, J. M.: Vascular Permeability Induced by Pancreatic Exudate Formed during Acute Pancreatitis in Dogs. Surg. Gynecol. Obstet., 143: 779, 1976.
43. Thal, A. P., Perry, J. F., Jr. and Egner, W.: A Clinical and Morphologic Study of Forty-two Cases of Fatal Acute Pancreatitis. Surg. Gynecol. Obstet., 105:191, 1957.
44. Trapnell, J. E.: The Natural History and Prognosis of Acute Pancreatitis. Ann. R. Coll. Surg., 38:265, 1966.
45. Wall, A. J.: Peritoneal Dialysis in the Treatment of Severe Acute Pancreatitis. Med. J. Aust., 2:281, 1965.
46. Wangensteen, O. H., Leven, N. L. and Manson, M. H.: Acute Pancreatitis (pancreatic necrosis). Arch. Surg., 23:47, 1931.
47. Waterman, N. G. and Walsky, R. S.: Transperitoneal Absorption of Amylase in Acute Experimental Pancreatitis. Surg. Gynecol. Obstet., 131:729, 1970.
48. Weissberg, D., Adam, Y. G., Volk, H. and State, D.: Acute Pancreatitis: A 10-Year Study. Am. Surg., 38:574, 1972.
49. Whalen, J., Rush, B., Albano, E. and Lazaro, E.: Fatal Acute Pancreatitis. Am. J. Surg., 121:16, 1971.
50. Wilkinson, E. J.: Acute Pancreatitis in Pregnancy. Obstet. Gynecol. Surg. 28:281, 1973.

DISCUSSION

DR. GEORGE L. JORDAN, JR. (Houston, Texas): This paper is of significance, because only 20 years ago pancreatic trauma was rare, and when we first reviewed our experience, we were seeing only two or three cases a year. Currently, we see about 40 cases a year, and I recently had reason to review a series of cases similar in size to that reported by Dr. Jones.

Through these 20 years, many papers have been published on small groups of cases, and many techniques were developed. It is only, however, when a series such as Dr. Jones' is analyzed in detail that the overall problem can be assessed so that relatively definitive conclusions are possible. We are indebted to Dr. Jones for this fine presentation today, and I urge all of you interested in the subject to read his total manuscript in detail.

I would like to emphasize the point that he last made; namely, that conservatism really is the keynote of the treatment of pancreatic trauma. That doesn't mean that resection is never indicated. In many instances, resection is mandatory because of devitalization of the pancreas, and the Whipple operation and even total pancreatectomy may be necessary. On the other hand, most of the patients can be treated by drainage or by reconstruction with a Roux-en-Y loop.

I have reviewed 56 cases of total transection of the pancreas, both from penetrating and blunt trauma, and our lowest mortality rate has been in those treated conservatively. This is partly, of course, because of the severity of trauma which necessitated resection; but we have had no deaths among the patients who were treated by Roux-en-Y drainage of the caudal end of the pancreas.

I do not believe that we need to drain both ends. The proximal end can be closed and the distal end drained into the Roux-en-Y loop.

The mortality rate of pancreatic trauma is primarily related to multiple organ injury; and as indicated in this paper, most of the deaths occur in the first 24 hours. In our own experience, as in his, if only the pancreas is injured or no more than two other organs, the mortality rate is quite low. In a recent series of 100 cases that I reviewed, our overall mortality rate, fortunately, had been reduced to 14%.

The pancreas is rarely the cause of death immediately, and thus, in general, in a patient with multiple injuries, the pancreas should be treated last. It rarely causes massive hemorrhage from the pancreas *per se*. Severe hemorrhage is from the major vessels in close proximity. Thus, in general, one will treat the other lesions first and the pancreas last. If the patient is unstable, I agree completely that one may just drain the pancreas.

On the other hand, when the patient is stable, there are multiple procedures which one may choose, and it's only with this type of review that we can choose the best procedure for each individual patient.

DR. FRANK C. SPENCER (New York, New York): In reviewing experiences with pancreatic fistula following trauma at our staff conference at New York University about one and a half years ago, a review of published experiences found that in a series of 234 distal pancreatectomies, the frequency of pancreatic fistula varied from 13–30%. On closer analysis, the principal problem seems to be that of finding and securely closing the transected pancreatic duct. The problem was often compounded by hemorrhage in devitalized, contaminated tissue. The two questions that arose were: How to find the transected pancreatic duct and does the method of closure in this contaminated, devitalized field influence the frequency of fistula formation, considering the choices of an absorbable suture, silk or Dacron, or staples?

Dr. Leon Pachter in our Department of Surgery has investigated this problem in some detail in the past year and prepared the data showed on these three slides. In 12 patients undergoing distal pancreatectomy, the end of the transected pancreas has been closed with the stapling device. This is the standard TA-55 stapler, which inserts one row of 3.5 mm staples. As all of you know, we are all indebted to Dr. Mark Ravitch for introducing and popularizing the stapling concept in this country several years ago, with modifications of the techniques employed in Russia.

The crucial point in the use of the stapler is that it is applied to healthy pancreatic tissue. [Slide] Subsequently, the tissue beyond the staples is amputated but not oversewn. A drain is left in place for about five to eight days. With the nine cases, eight recovered uneventfully. One patient developed a fistula who had an associated injury of his portal vein, inferior vena cava and developed massive ascites following ligation of his portal vein. As Dr. Jordan previously indicated, much of the morbidity with pancreatic injuries is related to the associated injuries.

DR. JOHN L. CAMERON (Baltimore, Maryland): I believe this series of 400 or 500 patients with acute pancreatitis probably represents the largest group of well-studied patients with acute pancreatitis in this country. I think the ability to identify patients as the authors do as soon as they come into the hospital on the basis of prognostic signs as to whether they will have severe or mild pancreatitis is a very important contribution.

I certainly agree with Dr. Spencer and Dr. Ranson that there are a large group of patients, the majority of patients with acute pancreatitis, who will recover without any treatment. We have performed prospective randomized clinical trials in the last several years evaluating antibiotic therapy and atropine therapy, and there has been a study from California evaluating the use of the nasogastric tube, and none of these modalities affect the course of acute pancreatitis in the over-whelming number of patients who present. And as Dr. Spencer stated, if you don't do anything to hurt the patient, the majority of them will recover.

However, there are a small group with a very high mortality, and I think that the present series of patients is the largest series of patients with severe pancreatitis treated with peritoneal lavage, and it gives us some hope of improving the survival in this group.

I know that Dr. Ranson some time ago started a prospective randomized trial evaluating the use of peritoneal lavage in severe episodes of pancreatitis, and I wonder if he would give us some details of that prospective study, and why it was terminated, since the data presented here, by and large, is retrospective analysis.

I rise mostly to discuss antibiotic therapy, however, in acute pancreatitis. We performed a study in 100 consecutive patients with acute pancreatitis several years ago, randomizing the use of ampicillin. Dr. John Sawyers presented a second study at this Association a year or two ago, again evaluating the use of ampicillin in acute pancreatitis. Both of our studies demonstrated that ampicillin was of no value in the treatment of acute pancreatitis, that the number of septic complications was not decreased, and those septic complications, when they occurred on ampicillin, were apt to be with resistent organisms.

I think this can be interpreted in one of two ways: either we used the wrong antibiotic, or else antibiotics should not be used. Ampicillin does not cover the majority of organisms that are responsible for causing pancreatic abscesses, and I wonder if the increase in late mortality, after the improvement in early mortality through peritoneal lavage, could not be decreased if, instead of ampicillin, possibly an aminoglycoside along with penicillin and clindamycin, or an aminoglycoside along with chloromycetin, were used, either prophylactically, parenterally, or, maybe even better yet, in the dialysis fluid.

Finally, I'd like to make one last comment. I think that the data available from the literature suggest that the Levin tube does not play a major role in influencing the course or the outcome, of acute pancreatitis. I think most large series of pancreatic abscesses demonstrate that there are two periods in which abscesses occur either immediately, in a very severe case in which there is massive pancreatic necrosis, or in the period of two or three weeks after the initial presentation, after, presumably, an initial sterile piece of infarcted pancreas becomes suprainfected. And I would think that that's why his patients who initially improved and began eating subsequently developed a pancreatic abscess, and that it was probably unrelated to the onset of eating and the absence of Levin tube suction for 14 days.

DR. ERNEST F. ROSATO (Philadelphia, Pennsylvania): When there were two Rosatos at the University of Pennsylvania, we had a very active interest in the treatment of pancreatitis by lavage. We studied this first in the laboratory with guinea pigs and with dogs, and, interestingly, we found that lavage does improve survival when no other treatment was given; and, furthermore, it didn't particularly matter which way you administered it, either by operative placement of the catheter or by percutaneous placement.

When we applied this to humans, we used the operative placement of catheters because of Dr. Waterman's initial successes that had been reported the year before, and we treated approximately ten patients with an 80% survival. While we did not classify them according to this very nice classification, which was published a little bit later, the great majority, at least 80%, would have fallen within at least the 5 to 6 category, and several into the 7 to 8 category.

We had an 80% survival with the operative placement of catheters, and one thing we did was not to have a set period of time for lavage. We judged when to stop the peritoneal lavage by the amylase drainage from the catheter, and when it fell below 1000 units, we stopped lavage. We would then recheck it two days later, and if it were elevated again, we would begin lavage again. With this technique, we were required to treat some of the patients for as long as two to four weeks, and I think this might explain some of the late abscesses that are seen with this particular treatment modality.

I would like to ask Dr. Spencer what his end points were, and whether he thinks it would be worth a trial of this prolonged lavage, in view of the fact that the operative mortality remained quite high in this group of patients who do get operated upon.

DR. SAMUEL R. POWERS (Albany, New York): I would just like to raise a note of caution in discussing Dr. Jones' paper.

The group in Texas, has had an enormous experience in the recognition of pancreatic injury, and I think it's important to emphasize that those of us who don't see quite as large a number of cases may not recognize them easily, particularly in the presence of a retroperitoneal hematoma. Although it has been the teaching for a long time, and many surgeons still believe, that a stable, nonpulsatile retroperitoneal hematoma should be left alone, I would suggest that this is not the case, and that pancreatic injuries will be missed. We believe that all retroperitoneal hematomas above the level of the pelvic rim should be explored very carefully, because a missed pancreatic injury is a very bad injury indeed.

DR. RONALD C. JONES (Closing discussion): I know of no one more capable of discussing trauma than the group from Houston; and certainly Dr. Jordan speaks with experience. He's given us direction for the last 25 years in the approach to pancreatic trauma.

Implanting both ends of the pancreas into a Roux-en-Y limb is only advocated if extensive resection is required, and there is associated trauma or contusion to the head of the pancreas, which might result in pancreatic fistula from the proximal segment. Implanting the distal end of the pancreas into a Roux-en-Y limb, described by Dr. Letton, is otherwise a fast and acceptable procedure.

Dr. Spencer, the variation in incidence of pancreatic fistula in the literature, I think, relates to the definition utilized by many surgeons as to what constitutes a pancreatic fistula. We have arbitrarily defined it as a fistula which drains in excess of one month. However, there are some pancreatic fistulas that drain a shorter time, but with considerable volume.

Permanent suture material has always been used, rather than catgut, which might dissolve quickly in the presence of activated pancreatic juice. We do attempt to ligate the pancreatic duct, but I do not think that this will prevent a pancreatic fistula, because there are many smaller ducts which are not ligated at the time.

We attempt to fishmouth the distal end of the proximal pancreas and oversew this with permanent suture material. We have used both silk and proline, but have not analyzed it as to whether the incidence of fistula is more or less with either. Most will drain for at least two weeks.

I think the use of the stapler, as you outlined, is an excellent suggestion. It would probably give a much better closure of both major and minor pancreatic ducts, but I think the most important thing is to be certain that there is Penrose and sump drainage placed at the point of injury, so when a collection appears, there is suction to promptly relieve it and prevent the development of lesser sac abscesses.

The comments by Dr. Powers were certainly in order. Our review of retroperitoneal injuries following penetrating trauma indicated there were associated retroperitoneal injuries, in addition to the pancreatic injury in 63% of cases; whereas, following blunt trauma, they occurred in 16%.

We advocate exploration of all retroperitoneal hematomas, unless we are reasonably certain that we are dealing only with pelvic fracture, in which case we would leave the retroperitoneum closed.

Dr. John H. C. Ranson (Closing discussion): I'd like to thank the discussants for their comments. I particularly appreciate Dr. Rosato's comments, because the experimental and clinical studies of the Drs. Rosato stimulated our interest in evaluating peritoneal lavage in patients with severe pancreatitis.

Dr. Rosato commented that, in their experimental studies, it did not seem to matter whether the catheters were placed at operation or percutaneously, but I think that there's an important distinction between the experimental situation and the clinical situation. In the experimental studies, operation was required to induce pancreatitis, so that all of the animals had undergone laparotomy in any event. Dr. Rosato suggested leaving the catheters for longer periods of time. We have made an arbitrary cutoff at four days, principally because we have been worried about introducing infection into the peritoneal cavity around the catheter. His suggestion is well taken. It is possible that lavage would be more effective if we were bolder about leaving the catheters longer.

There are a couple of technical hazards of lavage which I think should be emphasized. The first is that most of these patients have severe respiratory distress, and the addition of 2 l. of additional peritoneal fluid may cause a significant deterioration in their respiratory status. Therefore, pulmonary function needs to be closely monitored and, in a number of instances, it has been necessary to decrease the volume and timing of the cycle to avoid undue respiratory problems. The second potential hazard is that the tonicity of the lavage fluid is maintained with glucose. Since impaired glucose tolerance is a feature of severe pancreatitis, quite marked hyperglycemia has occurred in some patients during lavage, and glucose levels need to be closely monitored.

Dr. Cameron, you questioned our use of antibiotics, and following your study and that of Dr. Sawyers, our plan has been to administer antibiotics to patients until the 48 hour evaluation period is over. In patients who have less than three signs, the antibiotics are then stopped. The two studies, yours and Dr. Sawyers', both primarily involved patients who had rather mild acute alcoholic pancreatitis. The efficacy of antibiotics in preventing late peripancreatic abscesses needs to be evaluated on a controlled basis in patients with more severe disease and those with biliary pancreatitis.

You asked about the randomized study. Our initial evaluation of lavage was in a randomized study that included five patients who were lavaged and five who were not. In that small study the periods of hyperamylasemia, leukocytosis, and hypocalcemia were quite markedly shortened in the lavaged group. The most important finding was that the mean period spent in the ICU was reduced from 17 days to eight days in the lavaged group. Finally, there was one death in a nonlavaged patient. The controlled trial was stopped because the next patient who came along had five signs after he had been in the hospital for 48 hours. At that time, he was deeply comatose. He was not hypovolemic, but had hypotension, with a blood pressure of 80 mm Hg, despite massive pharmacological support. He was anuric, and had an arterial Po_2 of 59 mm Hg in 100% oxygen with positive end expiratory pressure. Because of the dramatic early response that we had seen in the controlled trial, we couldn't persuade anybody to consider withholding lavage in this patient. Within a few hours of the institution of lavage, he began to make urine. The following day he was responsive to his name, and four days later, when lavage was discontinued, he was off the respirator, off all pharmacologic support of his blood pressure, and had no detectable neurologic deficit.

It was this type of patient, however, which brought us to consider the potential hazards of early feeding. This patient responded so dramatically that his nasogastric tube was removed, and oral feedings were resumed on the seventh hospital day. This was in contrast to a mean period NPO in patients with five signs of 21 days. About two days after he began feeding, this patient had a dramatic re-exacerbation of his disease, and developed late complications which eventually led to his death. We would have to agree with you that we don't know whether the early feeding produced this re-exacerbation or whether it would have occurred in any event. However, following the introduction of the arbitrary minimum period of fourteen days without oral feedings, there have been no deaths in the last nine patients treated with nonoperative lavage.

Results of Elective Duodenal Ulcer Surgery in Women:

Comparison of Truncal Vagotomy and Antrectomy, Gastric Selective Vagotomy and Pyloroplasty, Proximal Gastric Vagotomy

J. LYNWOOD HERRINGTON, JR., M.D., JOHN L. SAWYERS, M.D.

This study provides a retrospective comparative analysis of results in 90 women patients who underwent three different elective operations for intractable duodenal ulcer disease. Group I (30 patients) underwent truncal vagotomy/antrectomy (TV+A); Group II (30 patients) gastric selective vagotomy/pyloroplasty (GSV+P); and Group III proximal gastric vagotomy (PGV). There were no operative deaths among the 90 patients. No patient after TV+A has developed a recurrent ulcer. Two recurrent ulcers developed after GSV+P, and one gastric ulcer occurred after PGV. Dumping, diarrhea, and reflux gastritis were lower after PGV than with TV+A and GSV+P. Follow-up studies have been from six months to ten years. The clinical results among the three groups of women patients compare favorably with results obtained in a recent prospective randomized study using the identical operative procedures in three groups of men patients operated upon for intractability. There was no statistically significant difference between women and men after similar operative procedures, but the postgastrectomy sequelae were less after PGV in both women and men patients.

THROUGHOUT THE EXTENSIVE LITERATURE on the surgical treatment of duodenal ulcer, scant data exists comparing long-term results between men and women patients. Even rarer are reports dealing solely with results limited to women. Nevertheless the impression exists that long-term clinical results in women compare unfavorably with men, particularly when the indication for operation is intractability.

This study was designed to provide a retrospective comparative analysis of results among three groups of adult women who underwent different operations for chronic duodenal ulcer. In addition, clinical results are compared to results from a prospective randomized study of adult men with chronic duodenal ulcer who underwent the same duodenal ulcer operations. The principal indication for operation in each patient was intractability, and no patient with active bleeding, acute perforation, or obstruction was introduced into this study.

From the Department of Surgery, Vanderbilt University, and the Surgical Service of St. Thomas and Metropolitan Nashville General Hospitals, Nashville, Tennessee

Clinical Material

The 90 women in this study were divided into three groups of 30 patients each. Group I (average age 49 years) underwent truncal vagotomy+antrectomy (TV+A); Group II, gastric selective vagotomy+pyloroplasty (GSV+P) (average age 40 years); and Group III (average age 45 years) proximal gastric vagotomy (PGV) (Fig. 1).

Follow-up studies on the patients extends from six months to ten years with the majority of patients being followed more than four years (Table 1).

Operating Techniques

The technique of truncal vagotomy+antrectomy has been previously described by us.[9,10,14] A 2–3 cm segment is excised from both the anterior and posterior vagal nerve trunk. Approximately 40% of the distal stomach is removed taking care that the distal resection extends beyond the pylorus. Gastrointestinal continuity is reestablished by the Schoemaker modification of the Billroth I gastroduodenostomy.

Gastric selective vagotomy divides all vagal fibers to the stomach, but leaves the hepatic and celiac rami intact.[8] In addition, the dissection is carried cephalad 5 cm above the esophagogastric junction as is done with proximal gastric vagotomy. A Finney pyloroplasty was

---

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Reprint requests: John L. Sawyers, M.D., St. Thomas Hospital, P.O. Box 380, Nashville, Tennessee 37202.

Submitted for publication: December 8, 1977.

0003-4932-78-0500-0576-0085 © J. B. Lippincott Company

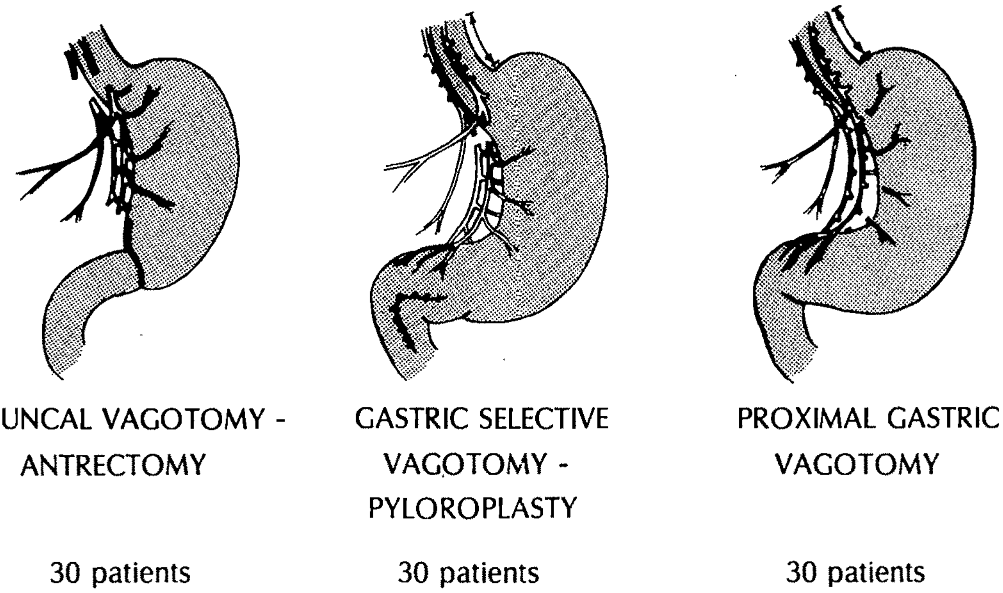

TRUNCAL VAGOTOMY - ANTRECTOMY
30 patients
GASTRIC SELECTIVE VAGOTOMY - PYLOROPLASTY
30 patients
PROXIMAL GASTRIC VAGOTOMY
30 patients

FIG. 1. Retrospective Study—90 female patients.

used as the complementary drainage procedure in all patients.

The technique of proximal gastric vagotomy has been identical to that described by Goligher and Johnston.[6,12] The entire lesser gastric curve is freed of all neurovascular attachments beginning cephalad to the antral parietal border as defined by the insertion of the anterior nerve of Latarjet onto the lesser curvature (Crow's foot) and extending 5–6 cm cephalad to the gastroesophageal junction. The anterior and posterior nerves of Latarjet supplying the gastric antrum and the hepatic and celiac branches are left intact. The criminal nerve of Grassi, from the posterior vagal trunk to the gastric fundus,[7] is divided, and the distal esophagus carefully circumscribed to divide any vagal fibrils running down the esophageal wall. As a final step, the lesser gastric curve is imbricated by approximating the anterior and posterior walls.

Hospital Complications

There was no operative or hospital mortality among the 90 patients. One patient in the PGV group died six months following operation of unrelated causes and is included in the follow-up data. There have been no additional deaths during the long-range study.

In the TV+A group, two patients had significant wound infections, and one patient developed a pulmonary embolus but survived. No other patient among the three groups has had a suspected or proven pulmonary embolus or significant respiratory or cardiac complication during hospitalization. Among the GSV+P patients one wound infection occurred. In the PGV group, one patient underwent iatrogenic splenectomy and developed a left subphrenic abscess requiring drainage. Two additional patients developed minor wound infections (Table 2). Ten of the 30 PGV patients (33.3%) upon careful questioning experienced epigastric fullness and early satiety. In five of these patients, symptoms disappeared completely in two to three weeks, but in the remaining five, mild symptoms extended into the long-range follow-up in four, and one patient required reoperation for poor gastric emptying.

Results

The one patient in the PGV group who died six months postoperatively after a sudden episode of nonocclusive mesentric vascular disease had obtained an excellent clinical result up to the time of her fatal illness. All other patients have been followed closely by repeated examinations, including clinical evaluation, gastrointestinal roentgen studies, endoscopy, and gastric secretory analysis when indicated.

TABLE 1. *Length of Follow-up*

	TV + A	GSV + P	PGV
	No. Pts.	No. Pts.	No. Pts.
9–10 yr		1	
8–9 yr		1	
7–8 yr		2	
6–7 yr		6	
5–6 yr		4	
4–5 yr	14	5	6
3–4 yr	6	5	7
2–3 yr	5	6	7
1–2 yr	5	0	4
6 mo to 1 yr	0	0	6
	30	30	30

TABLE 2. *Mortality–Morbidity*

	TV + A	GSV + P	PGV
Operative mortality	0	0	0
Wound infection	2	1	2
Pulmonary embolus	1	0	0
Subphrenic abscess	0	0	1

TABLE 4. *Long-range Sequelae*

	TV + A	GSV + P	PGV
Dumping	(6) 20%	(7) 23%	(1) 3%
Diarrhea	(5) 17%	(2) 7%	(1) 3%
Epigastric fullness	(3) 10%	(2) 7%	(5) 17%
Reflux gastritis	(5) 17%	(3) 10%	(0) 0%
Weight loss	(3) 20%	(2) 7%	(0) 0%

Results have been recorded using the Visick classification with Visick I (excellent result) representing the patient who is free of all gastrointestinal complaints and is in an excellent nutritional state. Visick II (good result) represents a patient with mild fullness, mild diarrhea, or occasional dumping. The patient is free of ulcer disease and in excellent nutritional state. The Visick III (fair result) represents a patient with appreciable dumping symptoms, significant reflux gastritis, and/or moderate diarrhea. A Visick IV (poor result) indicates the patient with recurrent ulcer, severe nutritional deficits or severe postgastrectomy problems.

Results, tabulated in Table 3, have been analyzed by our biostatistical department. The Visick I grading in the PGV group (77%) represents a statistically significant difference ($p < 0.5$) over the Visick I grading in the TV+A and GSV+P groups. No other significant difference exists in the overall clinical results. Although satisfactory results (Visick I and II) were obtained in 97% of the PGV group, there was no significant difference between these and those in the TV+A or GSV+P groups as regards excellent and good results (Visick I and II).

Long-range Sequelae

Long-range complications are recorded in Table 4. The incidence of dumping was less after PGV when compared to both TV+A and GSV+P. With the latter two operations, the dumping syndrome occurred with almost equal frequency. No patient, however, experienced dumping to a severe or incapacitating degree. Diarrhea was less in patients who had PGV and GSV+P and higher after TV+A. Because of the small number of patients having diarrhea, the statistical evaluation showed only a borderline difference between PGV and TV+A as regards the incidence of diarrhea ($p = .07$). Seventeen per cent of patients experienced mild to moderate diarrhea after TV+A, but no patient developed severe diarrhea.

TABLE 3. *Overall Clinical Appraisal*

	TV + A		GSV + P		PGV	
Visick I	(16) 53%	83%	(15) 50%	90%	(23) 77%*	97%
Visick II	(9) 30%		(12) 40%		(6) 20%	
Visick III	(2) 7%		(1) 3%		(0) 0%	
Visick IV	(3) 10%		(2) 7%		(1) 3%	
	30 Pts.		30 Pts.		30 Pts.	

* $p < .05$.

Persistent epigastric fullness has been more common in patients who had PGV than TV+A or GSV+P. Four of the five patients in the PGV group continue to experience mild fullness over a one to three year follow-up. One patient experienced severe epigastric fullness and delayed gastric emptying which necessitated antral resection six months following the initial operation (Figs. 2 and 3). She is now doing well almost four years postresection, but is classified as a poor result (Visick IV).

There is a significant difference in the incidence of reflux gastritis with TV+A and GSV+P when compared to PGV. Of the five patients in the TV+A group with reflux, symptoms were of such severity in three that Roux-en-Y diversion became necessary. These three patients represent poor results (Visick IV). The two remaining patients are currently being managed medically and are classified as fair results (Visick III). The three patients in the GSV+P group have mild reflux symptoms and are being managed by conservative means.

Weight loss has not been a major problem after any of the three operative procedures. No patient after PGV has lost weight, and actually five of the 30 patients have gained weight. No excessive weight loss has occurred after TV+A or GSV+P.

Recurrent Ulcer

Frequent and thorough evaluations during the follow-up study have shown that no patient after TV+A has developed a proven or suspected recurrent duodenal ulcer. Likewise, no gastric ulcer has occurred in the group (Table 5).

Among the GSV+P patients, one recurrent duodenal ulcer and one gastric ulcer have developed. The recurrent duodenal ulcer became manifest by the onset of epigastric pain five years postoperative in a 27-year-old patient. The ulcer was demonstrated by both x-ray study and endoscopy. Treatment consisted of antral resection.

The gastric ulcer occurred in a 31-year-old patient seven years postoperative. It was manifest by the onset of epigastric pain, and the ulcer was located on the posterior wall of the distal antrum. The duodenal ulcer had remained healed. There was no evidence of gastric stasis and the patient had received no ulcerogenic medication. The Hollander test which had been negative following GSV + P had reverted to positive. At reoperation an intact nerve fiber was found on the posterior esophageal wall coursing down to the gastric fundus. The nerve was divided and the gastric selective vagotomy was converted to truncal vagotomy. The gastric antrum was then removed. The patient has done well since this procedure which was carried out over three years ago. The nerve coursing along the posterior esophageal wall probably represented the criminal nerve of Grassi which is the most cephalad of the gastric nerve fibers originating from the posterior nerve of Latarjet. Both of these patients are listed as poor results (Visick IV).

No recurrent duodenal ulcer has developed in the PGV group. The patient with epigastric fullness and gastric stasis previously alluded to was also found on endoscopy to have a 3 mm superficial antral ulcer, but the duodenal ulcer had remained healed (Table 5). She has been recorded a poor result (Visick IV).

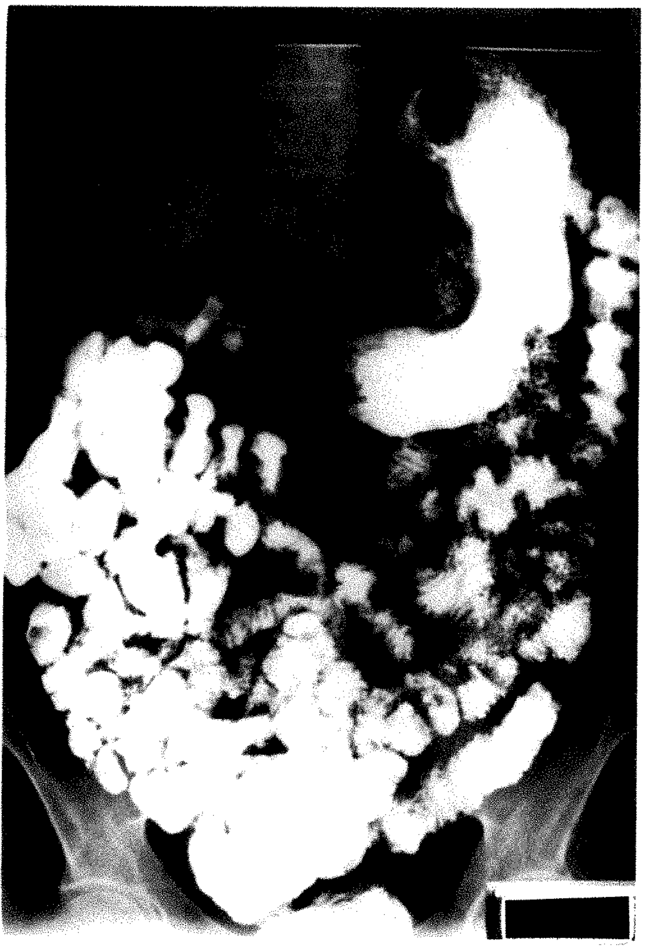


FIG. 2. Upper gastrointestinal barium study showing gastric retention following PGV.

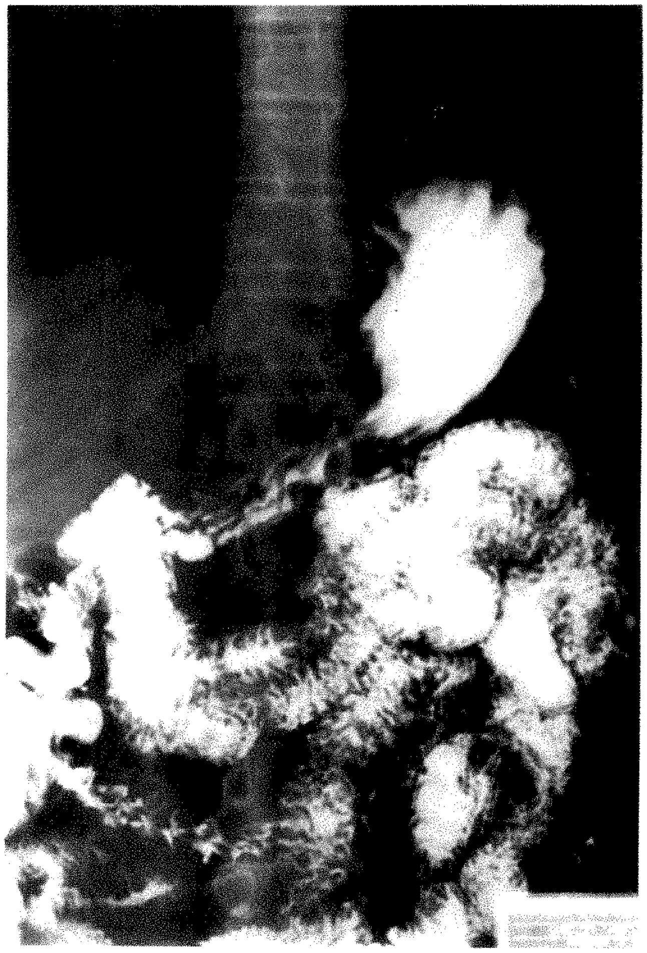


FIG. 3. Upper gastrointestinal contrast study in the same patient following antral resection with a Billroth I reconstruction.

Gastric Secretory Data

Postoperative gastric analysis was done in the TV + A and the PGV groups only if circumstances arose which warranted such studies. In the GSV + P group, 63% of patients were subjected to the Hollander test. Seventeen patients had negative response and two patients demonstrated an early positive response, but neither has developed a recurrent ulcer. Two of the 17 patients with a negative test during the early postoperative pe-

TABLE 5. *Recurrent Ulcer*

	TV + A	GSV + P	PGV
Duodenal ulcer	0	1	0
Gastric ulcer	0	1	1

TABLE 6. *Comparative Results — Women vs. Men*

TV + A					
Women			Men		
Visick I	16 (53%)	83%	Visick I	28 (56%)	94%
Visick II	9 (30%)		Visick II	19 (38%)	
Visick III	2 (7%)		Visick III	0 (0%)	
Visick IV	3 (10%)		Visick IV	3 (6%)	
	30 Pts			50 Pts	

riod later reverted to positive. One of these cases represents the patient who developed the gastric ulceration.

Comparative Results (Women vs. Men)

In a recently published prospective randomized study comparing TV+A, GSV+P, and PGV in adult men with duodenal ulcer intractability,[13] we found that excellent and good results (Visick I and Visick II) were obtained in 94% of patients with TV+A, 84% with GSV+P, and 96% with PGV.

In a comparison of clinical results with TV+A in women from this present study and in men from the prospective randomized study, we find that the excellent results (Visick I) in both groups are approximately equal, 53% and 56%. Although 94% of men obtained overall satisfactory results (Visick I and Visick II) as opposed to 83% for women, this is not statistically significant.

In comparison of women and men patients who underwent GSV+P, there was not a significant difference ($p = .05$) in Visick I grading, being 73% for men and 50% for women. The overall satisfactory results (Visick I and II) also show no significant difference (Table 7).

The Visick I and II grading, satisfactory results, after PGV were almost equal among men and women patients (Table 8). Also, in both sexes PGV was associated with less dumping, diarrhea, and reflux gastritis than TV+A and GSV+P (Table 9).

Discussion

Results of duodenal ulcer surgery in adult women have received little consideration in the literature. Some surgeons contend that the overall clinical results in women are inferior to men, but conclusions have largely been based on assumptions rather than comparative studies. Minimal or borderline indications for definitive ulcer operation may account for some of the unsatisfactory results. This has been our impression from evaluation of some of the women referred for consideration of remedial surgery for postgastrectomy sequelae. In Amdrup's current Mid Way reports[3,5] on 748 patients who had either GSV+P or GSV+A and PGV with or without drainage, he found no difference in the overall results between women and men patients.

In the present study women who had either TV+A or GSV+P obtained acceptable clinical results. The incidence of dumping after either operation did not differ appreciably from that in men. It is of interest that no women presented with either severe diarrhea or severe dumping. The most frequent unsatisfactory result in women with TV + A and GSV + P was reflux gastritis which is currently being recognized with greater frequency in both women and men.

Although sufficient time has not elapsed to evaluate long-term results of PGV, the 30 women in this study have done well during their six months to five year follow-up. Except for the complication of persistent epigastric fullness, the incidence of long-term sequelae has been remarkably low. Postprandial fullness is a frequent complication in both women and men after PGV. After each of the three types of vagotomy, intragastric pressure and transmural gastric tone are elevated, thus preventing the stomach from undergoing receptive relaxation and accommodation to distention. Fortunately, this problem is transient and disappears usually in a few weeks. Another reason for epigastric fullness after PGV may be related to the distal extent of the gastric denervation along the lesser gastric curve. If the antrum is denervated distal to the Crow's foot, gastric stasis and gastric ulceration may develop in a certain percentage of patients. For this reason, Amdrup[1,4] prefers a less extensive distal dissection than does Johnston[12] and leaves intact a 1–2 cm innervated segment of lesser curve cephalad to the Crow's foot.

The long-range effectiveness of PGV without drain-

TABLE 7. *Comparative Results — Women vs. Men*

GSV + P					
Women			Men		
Visick I	15 (50%)	90%	Visick I	27 (73%)	83%
Visick II	12 (40%)		Visick II	4 (11%)	
Visick III	1 (3%)		Visick III	5 (13%)	
Visick IV	2 (7%)		Visick IV	1 (3%)	
	30 Pts			37 Pts	

TABLE 8. *Comparative Results — Women vs. Men*

PGV					
Women			Men		
Visick I	23 (77%)	97%	Visick I	71 (83%)	96%
Visick II	6 (20%)		Visick II	11 (13%)	
Visick III	0 (0%)		Visick III	1 (1%)	
Visick IV	1 (3%)		Visick IV	3 (3%)	
	30 Pts			86 Pts	

TABLE 9. *Long-term Sequelae—Women vs. Men*

	Women			Men		
	TVA + A 30 Pts	GSV + P 30 Pts	PGV 30 Pts	TVA + A 50 Pts	GSV + P 37 Pts	PGV 86 Pts
Dumping	20%	23%	3%	22%	23%	1%
Diarrhea	17%	7%	3%	18%	3%	1%
Reflux gastritis	17%	10%	3	4%	5%	1%
Epigastric fullness	10%	7%	17%	0	8%	7%

age in preventing recurrent ulceration is unknown since the operation was first done only seven years ago. In Jensen's experience most ulcer recurrences (both women and men) appeared within 30 months, but he has recently observed a few recurrent ulcers develop after five to six years. In Jensen's five to eight year study, the recurrence rate is 9%.[11] Amdrup[2] predicts that the recurrent ulcer rate of PGV will approximate that of GSV+P.

This study indicates that definitive ulcer operations in women with intractable duodenal ulcer yield overall satisfactory results. There appears to be little difference in the comparative results of TV + A and GSV + P between men and women. PGV in both men and women is accompanied by fewer postgastrectomy sequelae than occur after either TV + A or GSV + P.

References

1. Amdrup, E., Clemmesen, T. and Andreassen, J.: Selective Gastric Vagotomy. Technique and Primary Results. Am. J. Dig. Dis., 12:351, 1967.
2. Amdrup, E.: Personal communication, 1977.
3. Amdrup, E., Andersen, D. and Høstrup, H.: A Mid Way Report on Primary Results in 748 Patients and Incidence of Sequels Following PCV and Selective Gastric Vagotomy. World J. Surg., in press.
4. Amdrup, E., Andersen, D. and Jensen, H.: Parietal Cell (highly selective or proximal gastric) Vagotomy for Peptic Ulcer Disease. World J. Surg., 1:19, 1977.
5. Andersen, D., Høstrup, H. and Amdrup, E.: A Mid Way Report on Reduction in Acid Secretion and Ulcer Recurrence Rate Following PCV and Selective Gastric Vagotomy. World J. Surg., in press.
6. Goligher, J. C.: A Technique for Highly Selective (parietal cell or proximal gastric) Vagotomy for Duodenal Ulcer. Br. J. Surg., 61:337, 1974.
7. Grassi, G. and Orecchia, C.: A Comparison of Intra-operative Tests of Completeness of Vagal Section. Surgery, 75:155, 1974.
8. Griffith, C. A.: Selective Gastric Vagotomy. Surg. Clin. North Am., 46:367, 1966.
9. Herrington, J. L., Jr.: Vagotomy-Antrectomy: Surg. Clin. North Am., 56:1335, 1976.
10. Herrington, J. L., Jr.: Vagotomy-Antrectomy for Duodenal Ulcer—Surgical Procedures. Warner-Chilcot Laboratories 3: 7, 1966.
11. Jensen, H. E.: One Hundred Patients, 5–8 Years After PCV. World J. Surg., in press.
12. Johnston, D. and Wilkinson, A. R.: Highly Selective Vagotomy without a Drainage Procedure in the Treatment of Duodenal Ulcer, Br. J. Surg., 57:289, 1970.
13. Sawyers, J. L., Herrington, J. L., Jr. and Burney, D. P.: Proximal Gastric Vagotomy Randomized with Vagotomy-Antrectomy and Selective Gastric Vagotomy-Pyloroplasty. Ann. Surg., 186:510, 1977.
14. Sawyers, J. L. and Herrington, J. L.: Vagotomy-antrectomy. *In* Harkins, H. N., Nyhus, L. M. and Wastell, C., Surgery of the Stomach and Duodenum. 3rd edition, Boston, Little, Brown and Company, in press.

DISCUSSION

DR. JONATHAN A. VAN HEERDEN (Rochester, Minnesota): We have felt for a long time that there is—and I might stress, fortunately—a distinct difference between men and women, as far as the results of peptic ulcer are concerned. It has been our clinical impression that women are more prone to postgastric surgery syndromes than men, and for this reason we have been somewhat reticent in performing resective procedures in women. This paper would suggest, and perhaps prove, that our belief has for many years been in error.

Along the same lines, we have felt that it is crucial to identify in both men and women the so-called "nervous puker" preoperatively; *i.e.*, the patient who is dumping before you operate on their stomach, for they will tolerate gastric surgery poorly indeed.

Fortunately for this group of people, and for perhaps all people with duodenal, and perhaps gastric ulcer disease, proximal gastric vagotomy has come on the scene. This operation is currently our procedure of choice for the surgical treatment of duodenal ulceration, with very few exceptions. We have performed this procedure now in just over 220 patients over the past five years, without any significant operative morbidity and no operative mortality.

Thus far, there have been three proved and three suspected recurrent ulcers, for a recurrence rate of approximately 3%. As Dr. Herrington stressed, though, the last word is not in, and I don't think that one can really talk about this operation before a much longer time has gone by.

The reduction in gastric acid secretion (slide) in our experience has been most gratifying. Here, for example, is a patient whose fasting pH was 1.5; basal acid output, 17.8; MAO, 36. Ten days later pH is 6.5, BAO is 0.38, and the MAO, 17.4.

(Slide) We wondered if we were doing the operation correctly, evaluated a series of patients, and found that our average decrease in BAO was 82%, in contrast to Dr. Goligher's group, in which it was 92%; so we thought we were doing not too badly. The average decrease in MAO was 58%, in contrast to Dr. Goligher's 51%.

I would like to ask the authors the following four questions. First, in the antrectomy group in this paper, 17% of women and only 6% of the men fell into the Visik 3 and 4 categories. Do the authors therefore agree that women tolerate resective procedures more poorly than men?

Secondly, why is peptic ulcer disease decreasing so?

Thirdly, do the authors use pre- and postoperative gastric analysis as a routine, or not?

And fourthly, do they share our current enthusiasm for proximal gastric vagotomy?

DR. PAUL H. JORDAN, JR. (Houston, Texas): One of the most interesting points made in this paper, which I think is contrary to popular belief, is the conclusion that the results of gastric surgery for duodenal ulcer are as good, or as bad, depending on how you want to look at it, in women as in men. For such a nondiscriminating conclusion, this paper would have qualified without difficulty for the program of the recent National Women's Congress in Houston.

Perhaps, as the authors point out in their manuscript, one of the reasons for the previously held view that women do not tolerate gastric surgery equally as well as men, is the fact that the indications for their surgery might sometimes have been minimal, or borderline.

Perhaps a similar line of reasoning may partially explain the apparent decrease in the number of patients seen with duodenal ulcer. This lesion may have gone down the endoscopic tube with increasing accuracy in the diagnosis provided by endoscopic examination.

We do not have experience with a group of women such as the authors have presented, but we do have a prospective evaluation of proximal gastric vagotomy in progress which has not been analyzed for statistical differences. However, in our first 200 cases of parietal cell vagotomy, or proximal gastric vagotomy, which include those performed in the prospective study, our results appear similar to the authors'. After five years the recurrence rate has been 4%, dumping, 9%, diarrhea, one-half per cent. While we have had no serious diarrhea or dumping after proximal gastric vagotomy or after selective vagotomy/antrectomy and Billroth I, which we are using for randomization, we do feel that dumping occurs less frequently and is much less of a problem or nuisance after proximal gastric vagotomy.

The ability of the patients to maintain their weight and their general feeling of well being also seems better after proximal gastric vagotomy.

What I'm concerned about is whether our data is going to show significant differences, indicating that proximal gastric vagotomy is a superior operation, or whether it will remain a subjective feeling, and therefore unconvincing to you.

Although Dr. Herrington has reported significantly greater numbers of excellent results after proximal gastric vagotomy than after other operations, he has indicated there was no statistical difference in the percent of excellent and good results, when taken together, between the three operations that they are reporting on. Also, he reported that there was no serious dumping or diarrhea after any of the operative procedures, although they occurred less frequently after proximal gastric vagotomy than after the other operations.

If the recurrence rate after proximal gastric vagotomy is likely to be higher than after truncal vagotomy and antrectomy, what, in his opinion, is the most important feature of proximal gastric vagotomy as he sees it that recommends the operation over truncal vagotomy and antrectomy?

DR. BERNARD W. THOMPSON (Little Rock, Arkansas): Last year at the meeting of this Association in Florida, Dr. Herrington convinced me that I should try some of these proximal gastric vagotomies in patients with the complications of duodenal ulcer. Therefore, during the past year we have carried out this operation, using his technique, in 20 patients. Unfortunately, these are all male.

It's not that we don't like women, but we just don't have any for patients in the Veterans Hospital.

We have had only one patient who has complained of postoperative bloating. In general, these patients have been very pleased with their operation. We haven't seen the problems that are usually associated with vagotomy and destruction of the pylorus; namely, reflux gastritis, dumping, and diarrhea.

We have had several patients, unfortunately, in whom we have found that the BAO and MAO have not fallen as dramatically as mentioned by Dr. Herrington. We are, therefore, concerned that this small number of patients may in the future develop recurrences that we are not now seeing.

I would like to ask Dr. Herrington if they have attempted any proximal gastric vagotomies in the patients that the British are now reporting; namely, those who have partial obstruction. And if so, are they having more trouble with bloating?

We have not tried the dilatation of the pylorus after doing the proximal gastric vagotomy, and I would like to know if they have any experience in this area.

DR. JOHN L. SAWYERS (Closing discussion): We carefully chose them ahead of time, and I think we selected well, because they essentially agree with us that proximal gastric vagotomy is superior for the surgical management of duodenal ulcer.

Certain questions were raised by Dr. van Heerden. The first question was regarding the Visick III patients who underwent antrectomy. The results were a little worse in women than men, and is this significant?

The figures are quite small—two women were in Visick III and no men. The statisticians cannot find a statistically significant difference because the numbers were too small.

The second question was: Why is peptic ulcer disappearing? I don't know.

The third question was: Do we do gastric analysis, pre- and postoperative? Yes, we do. We do it because we're interested in comparing the results pre- and postoperatively. We do not use the preoperative gastric analysis as a criterion for selecting the type of operation.

The question was raised about the patient who had partial obstruction. Can proximal gastric vagotomy be applied to that group of patients? It has been done by Johnston in Leeds. He cautions against its use. We have used PGV only in three patients with obstruction, dilating the obstruction through a gastrotomy opening, using the Hegar dilators. The results have been satisfactory in two of those patients, but in one patient we had to reoperate and do a drainage procedure.

We do think that we may have become popular with the women's liberation movement, because we have shown that women may enjoy equal rights with men for a good to excellent result following operation for duodenal ulcer. This study reinforces our enthusiasm for proximal gastric vagotomy as the operation of choice for duodenal ulcer. PGV is safe and is accompanied by low morbidity. We're now seeing a lot of happy patients who are not made worse by an operation intended to help them.

Smooth way to rough it.

Our natural-fiber, bulk-producing laxative is the easy way to give your patients the roughage they need. In constipation, whether simple or associated with such conditions as diverticular disease, irritable bowel syndrome or hemorrhoids, Metamucil leads to the soft life.

The powder mixes with water or juices; the Instant Mix is citrus-flavored. Deliciously easy to take.

Metamucil®
brand of
psyllium hydrophilic mucilloid

SEARLE Searle Laboratories
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

661

FACULTY POSITIONS

College of Medicine, King Faisal University
Dammam, Saudi Arabia

Applications invited from qualified men and women in General Surgery. American Board certification in surgery (or equivalent in Canada or Great Britain) plus teaching experience required. Language of instruction is English. Positions available in September 1978; interviews scheduled with the Dean in the United States early in 1978.

Salary ranges: (Given monthly in Saudi Riyals followed by approximate annual equivalent in U.S. dollars)

	Academic Salary	+ *Clinical Bonus of 50%*	= *Total Approximate yearly dollars*
Professor:	SR 6,000-6,600	SR 3,000-3,300	($30,500-33,500)
Assoc. Prof.:	SR 4,800-5,800	SR 2,400-2,900	($24,400-29,400)
Assist. Prof.:	SR 3,600-4,600	SR 1,800-2,300	($18,300-23,400)

Benefits include free furnished accommodations and annual leave with travel allowance to country of origin.

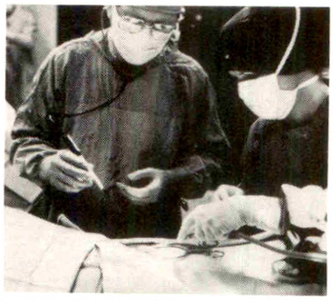
No Saudi income tax is imposed.

Send curriculum vitae and references with addresses and telephone numbers to:

Mohammed T. Altorki, M.D., MRCP
Dean of the Medical Faculty
King Faisal University
c/o Saudi Arabian Educational Mission
2223 West Loop South, Suite 400
Houston, Texas 77027

Specify dates of teaching appointments and availability.

NEW MINIATURIZED DOPPLER



The Doplette® 10 portable Doppler probe is a completely self-contained pen-sized Doppler device that transforms a standard stethoscope into a tool with significant new diagnostic usefulness. Because the Doplette 10 can be gas sterilized, it becomes a valuable adjunct to the surgical suite. And, with shirt-pocket convenience and diagnostic capability, its versatility is extended to office, clinic or patient rounds for a wide variety of vascular applications. Includes batteries and cassette tape of typical Doppler sounds. For more information contact:

Physio-Control®

11811 Willows Road, Redmond, Washington 98052
206/883-1181, Cable: PHYSIO-RED, Telex: 32-0166

Quick Reference To Surgical Emergencies

■

Edited by Gerald W. Shaftan, M.D.
and Bernard Gardner, M.D.

This handy manual, packed with clinical data in easy-to-use outline form, is designed for instant use in helping you evaluate the surgical emergency, make the diagnosis and carry out the indicated treatment.

Divided into two broad categories of traumatic and non-traumatic surgical emergencies the book systematically covers: Techniques of evaluating the patient and applying diagnostic criteria . . . Radiologic procedures that are necessary . . . Anesthesia considerations . . . Fluid and electrolyte replacement.

The patient evaluating techniques, diagnostic steps and surgical treatment are presented step-by-step with each individual entry numbered for simplicity.

Subject matter includes emergencies occurring in the areas of general, orthopaedic, neurologic, ophthalmic, thoracic, plastic, urologic, head and neck, and pediatric surgery.

All who are involved in surgical emergency treatment will appreciate this easy-to-use, time-saving manual.

664 Pages • 50 Illustrations • 1974
Flexible Binding • $23.75

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:
☐ QUICK REFERENCE TO
SURGICAL EMERGENCIES $23.75

Name ______________________

Address ______________________

City ______________ State ________ Zip ____

☐ Payment enclosed (Save postage & handling) ☐ Charge and bill me (Plus postage & handling)

Also available at your medical bookstore. AS 5/78

Tablets
Percocet®-5 C II

DESCRIPTION Each tablet of PERCOCET®-5 contains 5mg oxycodone hydrochloride (WARNING: May be habit forming), 325mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories Inc
Subsidiary of the DuPont Company

DU PONT

FOR MODERATE TO MODERATELY SEVERE PAIN

Acetaminophen with the narcotic difference

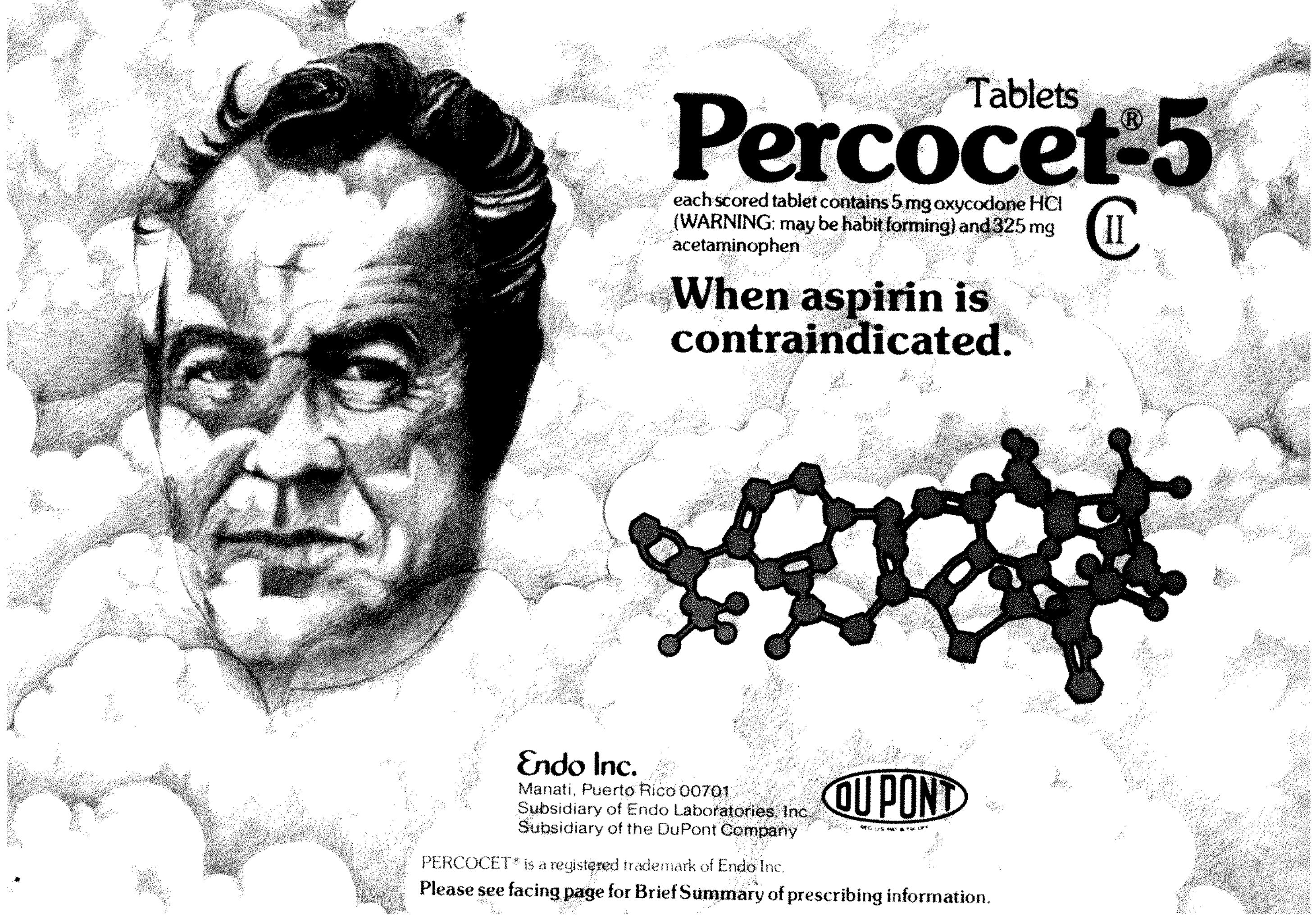
Reliable oral narcotic analgesia...

The narcotic component in PERCOCET®-5 is oxycodone, which is readily absorbed and provides dependable oral analgesia—usually within 15 to 30 minutes. Oxycodone can produce drug dependence of the morphine type and should be prescribed with the same degree of caution appropriate to the use of other narcotic-containing medications.

...aspirin free

Acetaminophen is a non-narcotic analgesic widely used for aspirin-sensitive patients. Equivalent to aspirin in analgesia, it complements the pain relief provided by oxycodone.

The usual dose of PERCOCET®-5 is one tablet every six hours, providing convenience and economy for your patients. PERCOCET®-5 is ideally suited for your patients with aspirin sensitivity, with hemostatic disturbance, with peptic ulcer or on anticoagulation therapy.



Tablets
Percocet®-5

each scored tablet contains 5 mg oxycodone HCl (WARNING: may be habit forming) and 325 mg acetaminophen Ⓒ II

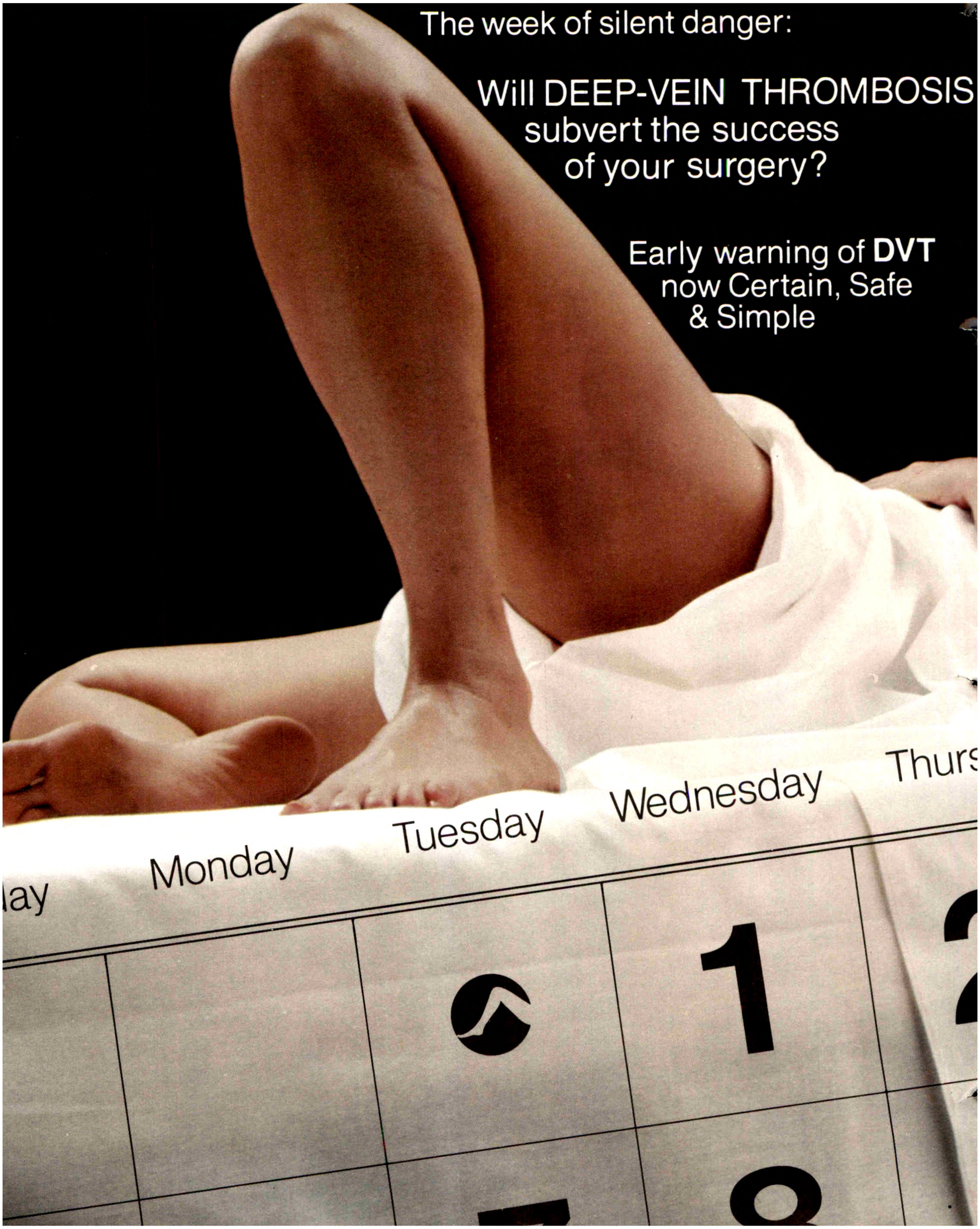
When aspirin is contraindicated.

Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories, Inc.
Subsidiary of the DuPont Company

DU PONT

PERCOCET® is a registered trademark of Endo Inc.

Please see facing page for Brief Summary of prescribing information.


The week of silent danger:
Will DEEP-VEIN THROMBOSIS subvert the success of your surgery?
Early warning of **DVT** now Certain, Safe & Simple
ay
Monday
Tuesday
Wednesday
Thurs
1
8

New

IBRIN System

from Amersham

IBRIN®
Radionuclide-Labeled
(^{125}I) Fibrinogen (Human)
IBRINITOR™
Portable Radioisotope Monitor

Deep-vein thrombosis (DVT) is thought to cause nearly 95% of the pulmonary emboli which contribute to over 50,000 post-operative deaths each year in the United States.*

Now, with Amersham's new IBRIN System, DVT can be detected and serially monitored even before any clinical symptoms are manifest... whether the thrombi are established or forming.

The IBRIN System is highly accurate, safe and easy to use, and minimizes patient discomfort. It consists of IBRIN, a Radionuclide-Labeled (^{125}I) Fibrinogen (Human) and the IBRINITOR, a portable radioisotope monitor.

CERTAIN The diagnostic accuracy of IBRIN in the detection of DVT has been confirmed in more than 100 studies which showed a 92% correlation with venograpny. IBRIN actively participates in thrombus physiology; its consistent clottability insures bioactivity and allows accurate detection of both established and lysing thrombi.

Controlled clinical studies were conducted to establish the safety and efficacy of IBRIN. In 111 initially reported studies, venograms were obtained for correlation with the fibrinogen study results. (Table 1.)

Table 1: *Correlation of fibrinogen study with venogram for the detection of deep vein thrombosis in 111 cases* †

Fibrinogen Results	Venogram Results	
	Positive	**Negative**
Positive 27	24	3
Negative 84	6	78

Of these 111 studies, 66 were performed as diagnostic studies on patients suspected of having established deep vein thrombosis. The correlation of the fibrinogen study and venography in these studies is presented in Table 2.

Table 2: *Correlation of fibrinogen study with venograms for the detection of established deep vein thrombosis in 66 cases* †

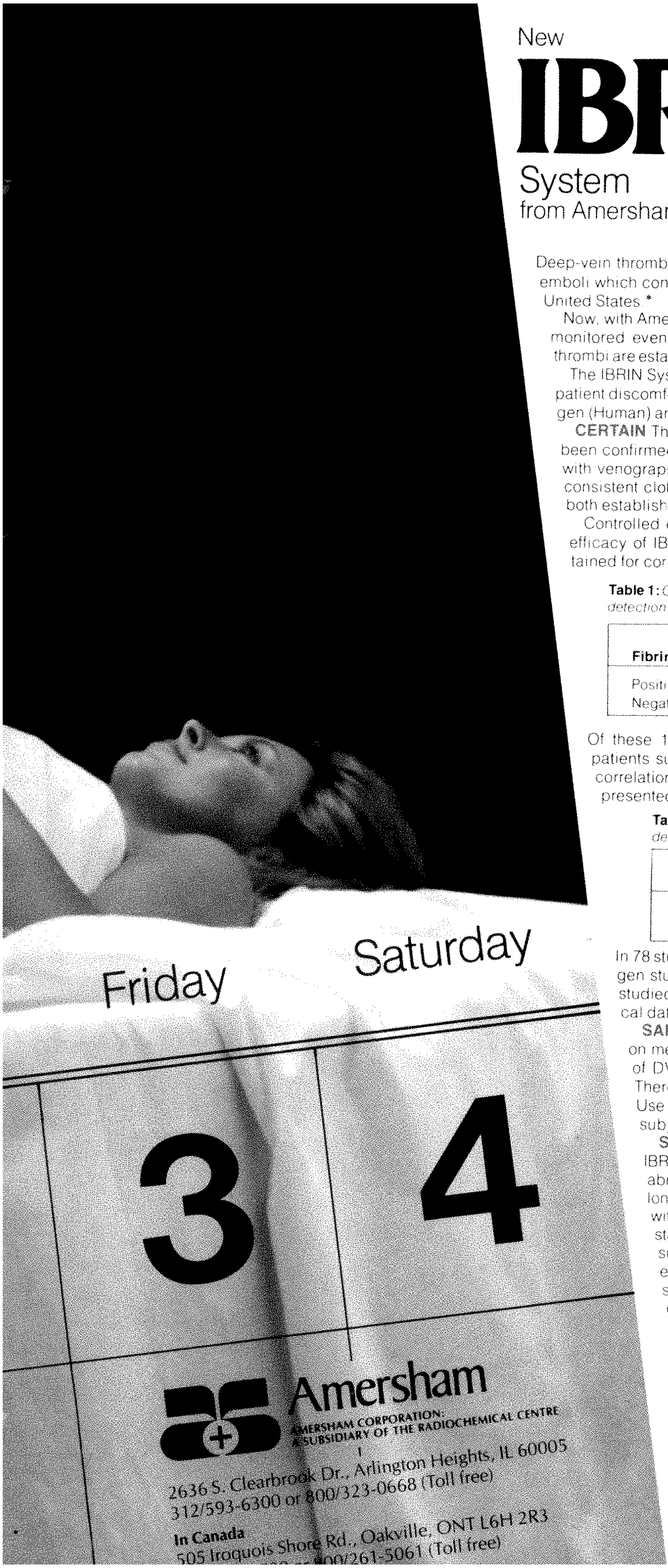
Fibrinogen Results	Venogram Results	
	Positive	**Negative**
Positive 17	16	1
Negative 49	4	45

In 78 studies without venogram correlation, the results of the fibrinogen study were positive in 17% and negative in 83% of the cases studied. These test results were consistent with all available clinical data on these patients.

SAFE DVT monitoring with the IBRIN System can be performed on medical, surgical and orthopedic patients. The IBRIN System of DVT detection is easily performed at the patient's bedside. There is no need to move the patient to a special procedural area. Use of the IBRIN System for detection of DVT reduces the need to subject the patient to the risks of radiopaque venography.

SIMPLE The patient is intravenously injected with 100 μCi of IBRIN. Monitoring can begin within three hours after injection and abnormal results can be confirmed within 24 hours. IBRIN has a long *in vivo* half-life, permitting monitoring up to seven days without additional injections. Serial monitoring allows for constant updating of the patient's status. The IBRINITOR is ideally suited for monitoring large numbers of patients quickly and easily. The electronic design assures reliable accumulation of statistically valid data and eliminates most operator error. A data printout insures ease and accuracy of data collection. These, plus many other design features of the IBRINITOR, make it a dramatic improvement in DVT detection and monitoring. The IBRIN System is a complete mode of DVT detection that minimizes the need for venography and contrast dyes. Accurate results are obtained with fewer complications and minimum patient discomfort.

Contact your Nuclear Medicine Department for details on how the IBRIN System can benefit your post-surgical patients.



Amersham
AMERSHAM CORPORATION:
A SUBSIDIARY OF THE RADIOCHEMICAL CENTRE
2636 S. Clearbrook Dr., Arlington Heights, IL 60005
312/593-6300 or 800/323-0668 (Toll free)

In Canada
505 Iroquois Shore Rd., Oakville, ONT L6H 2R3
800/261-5061 (Toll free)

---

*Kakkar, V.V. "Deep Vein Thrombosis Detection and Prevention." *Circulation*, Volume 51, January 1975.

†Write or Phone for Complete Information

See following page for brief summary of package insert.

The
IBRIN
System

IBRIN®
Radionuclide-Labeled
(^{125}I) Fibrinogen (Human)
IBRINITOR™
Portable Radioisotope Monitor

INDICATIONS
IBRIN is indicated for use in prospective studies for the early detection and subsequent monitoring of developing deep-vein thrombosis and in diagnostic studies for the detection of established thrombosis in the legs.

A. The IBRIN [Radionuclide-Labeled (^{125}I) Fibrinogen (Human)] test is indicated in patients with signs and/or symptoms suggestive of deep-vein thrombosis with or without associated pulmonary embolism or in patients with pulmonary embolism, with or without evidence of peripheral deep-vein thrombosis. In patients with established, old or "inactive" thrombi, the test will be positive only if radionuclide-labeled fibrin deposition occurs in a sufficient quantity to allow detection. Its use is not contraindicated in patients on anticoagulants.

B. The IBRIN [Radionuclide-Labeled (^{125}I) Fibrinogen (Human)] test is indicated for the detection of thrombus formation in patients undergoing major orthopedic or other surgical procedures, myocardial infarction, pulmonary disease, malignant disease and other medical conditions known to predispose to thromboembolism.

CONTRAINDICATIONS
There are no known contraindications to the use of IBRIN. However, it should be noted that the iodides given to block the uptake of ^{125}I by the thyroid gland are contraindicated in patients with a known sensitivity to the iodides.

WARNINGS
This radiopharmaceutical should not be administered to patients under 18 years of age, to patients who are pregnant, or to patients who are lactating, unless the information to be gained outweighs the potential risk.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of child bearing capability should be performed during the first few (approximately 10) days following the onset of menses. Nursing mothers should substitute formula feeding after the administration of Fibrinogen ^{125}I.

Extraordinary precautions have been taken in the preparation of IBRIN [Radionuclide-Labeled (^{125}I) Fibrinogen (Human)] to eliminate the possible transmission of hepatitis. Nevertheless, the remote risk of hepatitis associated with the administration of Radionuclide-Labeled (^{125}I) Fibrinogen (Human) cannot be entirely eliminated. The finding of viral hepatitis in any patient up to six months after the administration of IBRIN should be reported to Amersham for further evaluation, since there are numerous possible sources of hepatitis infection.

PRECAUTIONS
Care should be taken to insure minimum radiation exposure to the patient, consistent with proper patient management, and to insure minimum radiation exposure to occupational workers.

This drug contains radioactive materials which must be handled only by qualified personnel in conformity with Nuclear Regulatory Commission, agreement state, or other appropriate government regulations. Care must be taken to avoid excessive exposure to its radiation. Shielding or equivalent radiation protective measures must be used.

This product is prepared from units of human plasma which have been tested using RIA methods and found non-reactive for Hepatitis B surface antigen. Approved detection methods are not sensitive enough to detect all infectious units of blood or all possible cases of hepatitis. However, IBRIN has been prepared from single donor plasma and has been injected into recipients without incidence of fibrinogen related Hepatitis B as evidenced by periodic physical examination and laboratory testing (liver profile, CBC, and Hepatitis B surface antigen and antibody by radioimmunoassay) of the recipients.

There are a number of clinical circumstances requiring consideration in the interpretation of the test results. (See complete Package Insert.)

Fibrinogen ^{125}I scanning should preferably be performed prior to venography if both procedures are contemplated, since venography may cause increases in count rate making interpretation of post-venography monitoring data difficult.

Adequate reproduction studies on animals have not been performed to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Radionuclide-Labeled (^{125}I) Fibrinogen (Human) should be used in pregnant women only when clearly needed.

ADVERSE REACTIONS
There has been no reported incidence of allergic or anaphylactic reactions following the intravenous administration of IBRIN.

Amersham
AMERSHAM CORPORATION:
A SUBSIDIARY OF THE RADIOCHEMICAL CENTRE

2636 S. Clearbrook Dr., Arlington Heights, IL 60005
312/593-6300 or 800/323-0668 (Toll free)

In Canada
505 Iroquois Shore Rd., Oakville, ONT L6H 2R3
416/842-2720 or 800/261-5061 (Toll free)

New (5th) Edition!

Rhoads
TEXTBOOK OF SURGERY
Principles and Practice
●
Edited by JAMES D. HARDY, M.D.
with 279 contributors

Although technically a New (5th) Edition of *Surgery: Principles and Practice*, this revision is new in *title, editor, contributing authors, content, approach, and format*. It has been reorganized into three major parts: General Principles of Surgical Practice; Specific Lesions and Dysfunctions Involving Various Organs; and Parasurgical Considerations.

The approach is now problem-oriented and this outstanding volume considers virtually all current problems in surgery.

More than 270 contributors give you an enormous geographical and philosophical range in one volume. Each is well known in his field and discusses management of a specific problem. Included in each of the hundreds of topics discussed are basic features of the operation including a table of basic facts; an overview of the concept under discussion; description of specific pathological conditions; surgical history; physiology; a pathophysiological diagram and an anatomical sketch whenever feasible; many excellent illustrations of disease processes and treatment procedures; possible technical errors; safeguards; postoperative problems; and complications.

2354 Pages / 1738 Illustrations / 313 Tables
5th Edition, 1977 / One Volume Format: $38.50
Two Volume Format: $45.00

Now Available in Either One or Two Volume Form!

Lippincott
J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105
In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Rhoads TEXTBOOK OF SURGERY
☐ 1 Vol. $38.50 ☐ 2 Vols. $45.00

Name ______________________

Address ______________________

City ____________ State ________ Zip ________

☐ Payment enclosed ☐ Charge and bill me
(Save postage and handling) **(Plus postage and handling)**
Also available at your medical bookstore. AS 5/78

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

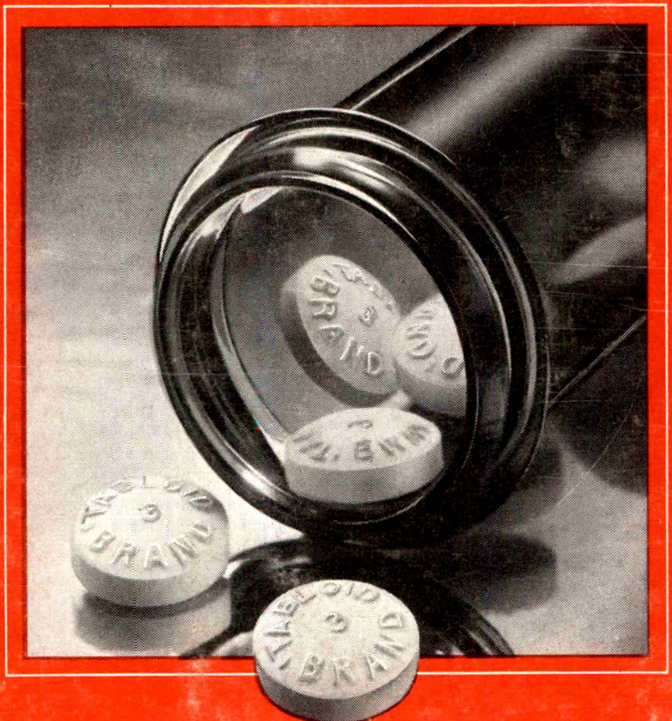
Abbott Scientific Products Division
 H-Big 53A
Amersham Corporation
 Ibrin 86A,87A,88A
Boehringer Ingelheim Ltd.
 Ducolax 11A
Bristol Laboratories
 Kantrex 22A,23A
 Prostaphlin 1A
Burroughs Wellcome Company
 Empirin Compound c Codeine .... Cover IV
Carnation Company
 Instant Breakfast 66A
Eaton Laboratories
 Vivonex 8A,9A
Endo, Inc.
 Percocet 84A,85A
Knoll Pharmaceuticals
 Dilaudid .... Cover II
Lederle Laboratories
 Amicar 12A,13A,14A
Eli Lilly & Company
 Keflin 54A,55A
Parke, Davis & Company
 Chloromycetin 4A,5A,6A
Pfizer Laboratories
 Vistaril I.M. 18A,19A,20A
A. H. Robins Company
 Phenaphen 44A,45A
Roche Laboratories
 Injectable Valium .... 72A thru 74A
Roche Products Inc.
 Dalmane .... 58A thru 60A
Searle Laboratories
 Metamucil 83A
Smith Kline & French Laboratories
 Ancef .... 48A thru 50A
 Compazine 62A,63A
E. R. Squibb & Sons, Inc.
 Velosef .... 68A thru 70A
Upjohn Company
 Cleocin Phosphate .... 38A thru 41A
USV Laboratories
 MVI 61A
Viobin Corporation
 Viokase 71A
Winthrop Laboratories
 Talwin Oral .... 24A thru 26A
 Injectable Talwin .... 80A thru 82A

SUPPLIES & EQUIPMENT

Arbrook, Inc.
 Surgical Gloves 17A
David Clark Company, Inc.
 Medical Anti-Shock Trouser 52A
Cooper Scientific Corporation
 Surgex Depilatory 21A
Deknatel
 Surgical Sutures 46A,47A
Dome Laboratories
 Paste Bandage 37A
Ethicon Inc.
 Skin Stapler .... 33A thru 36A
 Vicryl Sutures 64A,65A
W. L. Gore & Associates
 Vascular Grafts .... 27A thru 31A
Hollister Inc.
 Stoma Pouches 31A
Johnson & Johnson
 Lap Pad 42A,43A
Kendall Company
 Anti Embolism Stockings 67A
Life Sciences, Inc.
 Pulse Volume Recorder 57A
Lyne-Nicholson, Inc. Div. of
Advanced Instruments, Inc.
 Venodyne Intermittent Compression 77A
3M Company
 Steri Strip Skin Closures 75A
Medi Tech
 Embolic Agents 51A
Narco Pilling
 Clamps 32A
Radiological Assays Diversified, Inc.
 CEA Testing 65A
Physio-Control
 Portable Doppler 83A
Purdue Frederick Company
 Betadine Surgical 3A
Surgikos
 Absorable Hemostat 78A,79A
Winthrop Laboratories
 Phisohex 16A

MISCELLANEOUS

East Tennessee State University 14A
Jesse Jones Box Corporation 20A
King Faisal University 14A,83A
J. B. Lippincott Company 23A,56A,76A,84A,88A



EMPIRIN® COMPOUND
c̄ CODEINE

Each tablet contains: aspirin, 227 mg; phenacetin, 162 mg; and caffeine, 32 mg; plus codeine phosphate in one of the following strengths: #4—60 mg (gr 1); #3—30 mg (gr ½); #2—15 mg (gr ¼); and #1—7.5 mg (gr ⅛), (Warning—may be habit-forming).

CIII

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

२९.11.78

JUNE 1978 • VOL. 187, NO. 6
ISSN 0003-4932 ANSUA5

ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice

Since 1885

May and June numbers contain papers delivered at
THE 89TH ANNUAL SESSION
of the
SOUTHERN SURGICAL ASSOCIATION
Hot Springs, Virginia
December 5–7, 1977

1792

J. B. LIPPINCOTT COMPANY
PHILADELPHIA • TORONTO

Oral Dilaudid®
hydromorphone HCl CII

The first step after injectables in post-op analgesia.

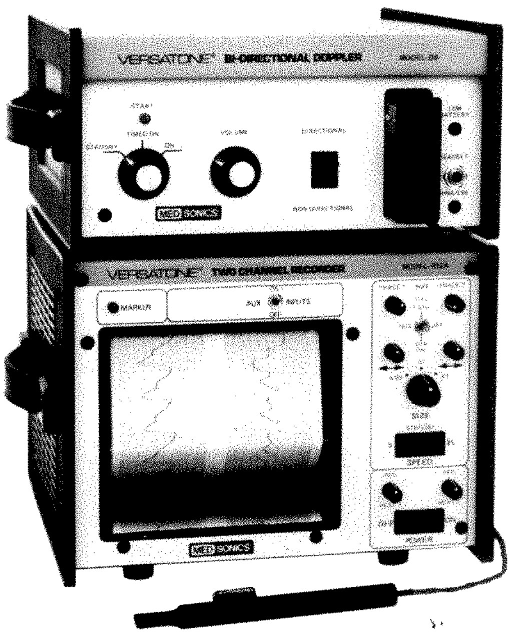
Description: Dilaudid is hydromorphone, a hydrogenated ketone of morphine.
Indications: For relief of moderate to severe pain.
Contraindications: Suspected increased intracranial pressure, status asthmaticus.
Warnings: May be habit forming with a potential for addiction equivalent to morphine in equi-analgesic doses. Tolerance may also occur. As with all narcotics, use in early pregnancy only when expected benefits outweigh risks.
Adverse Effects: Nausea, vomiting, diarrhea, constipation, anorexia and somnolence may occur although unlikely with appropriate dose selection.
Dosage and Administration: Dosage must be individualized. The usual adult dose is 2 mg every 4-6 hours, as necessary, for moderate to moderately severe pain. For more severe pain, 3-4 mg or more every 4-6 hours, as necessary, may be required.
Treatment of Overdosage: If overdosage is treated within an hour, emesis and gastric lavage should be attempted. Special attention should be given to respiration and, if depression occurs, it may be antagonized by the use of naloxone hydrochloride (Narcan®)—Endo, nalorphine hydrochloride (Nalline®)—Merck Sharp & Dohme or levallorphan tartrate (Lorfan®)—Roche, as recommended by the manufacturer. Other supportive measures should be applied when indicated.
How Supplied: Dilaudid HCl color coded tablets (NOT FOR INJECTION) imprinted with K logo on one side and potency on other side as follows: green—1 mg; orange—2 mg; pink—3 mg and yellow—4 mg Available in: 1 mg—bottles of 100 (NDC #0044-1021-02), 2 mg—bottles of 100 (NDC #0044-1022-02) and 500 (NDC #0044-1022-03), 3 mg—bottles of 100 (NDC #0044-1023-02), 4 mg—bottles of 100 (NDC #0044-1024-02) and 500 (NDC #0044-1024-03).

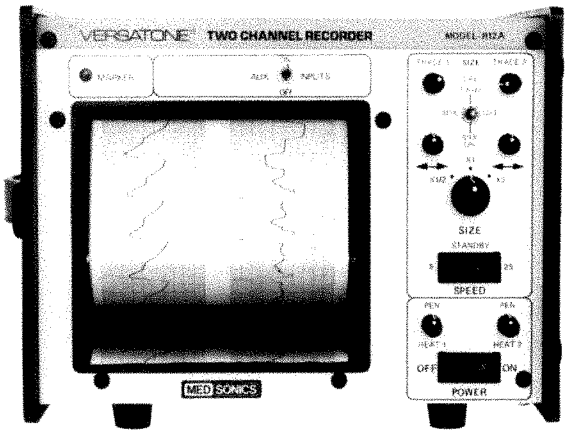
Knoll Pharmaceutical Company
Whippany, New Jersey 07981

Member Company, Certified Medical Representative Institute, Inc.

VERSATILE INSTRUMENTS FOR THE VASCULAR LABORATORY

VERSATONE® BI-DIRECTIONAL DOPPLER MODEL D9 Used with one of four plug-in probes, MedSonics Bi-directional Doppler employs ultrasound and the Doppler shift principle to detect blood flow and to distinguish the direction of flow. It provides explicit separation of advancing and receding blood flow, even in the presence of simultaneous flow in two directions. The Model D9 has a variety of outputs, including built-in loudspeaker, stereo headphones, tape recorder jacks, and calibrated outputs for graphic recording. Three pencil type probes (5MHz, 8MHz and 10MHz) and one flat probe (5MHz) suitable for taping in place are available.





VERSATONE TWO-CHANNEL CHART RECORDER MODEL R12A The VERSATONE two-channel Chart Recorder is used to chart the Doppler signals of forward and reverse blood flow from the Model D9 Bi-directional Doppler. This Recorder can also chart an ECG signal, by itself or mixed with a Doppler signal. An optional, built-in ECG preamp is available. In addition, the R12A accepts many other "high level" physiologic signals you may wish to record, including those obtained from MedSonics PPG equipment.

PHOTOPULSE® PPG SENSORS AND MODEL PA13 ADAPTOR The PHOTOPULSE photoplethysmograph (PPG) provides a sensitive means of detecting blood volume changes in the microcirculation close to the skin's surface. It may be applied to those parts of the body with good capillary beds, including digital pads, where it can be used to monitor pulse. The PPG also is used in a non-invasive procedure to detect significant obstruction of the extracranial internal carotid artery. Two PHOTOPULSE sensors are placed under a head band over each supraorbital area to record volume changes that occur when a series of compression maneuvers are carried out.

The PA13 adaptor allows the use of two PPG sensors with the R12A recorder or with other laboratory chart recorders.

For more information on these and other instruments for the vascular laboratory, call or write:

MEDA SONICS

MedSonics, Inc. • 340 Pioneer Way, P.O. Box M • Mountain View, CA 94042
Toll-free telephone 800 227-8076 • In California, call collect (415) 965-3333
Telex: 33-4448 • Cable: MEDASONICS

Osborn

Nip it in the gut.

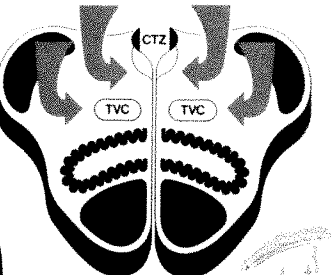
Torecan can help control nausea and vomiting with dual action:*
1) against circulating emetics (at the CTZ)
2) against emetic sights, emotions, and organ insults (at the TVC)

In using Torecan, the physician should consider the adverse reactions which are associated with the drug specifically and phenothiazines generally.**

- It's not for sedative use.
- It's not intended as a tranquilizer.
- It's not an antihistamine.
- It's not intended for psychotic symptoms.

*As shown in animal studies; TVC—True Vomiting Center, CTZ—Chemoreceptor Trigger Zone.

**Please see brief summary for detailed information concerning potential adverse reactions.



Torecan®

(thiethylperazine)

Injectable—10 mg/2ml (thiethylperazine malate, NF)
for IM injection only

Suppositories—10 mg (thiethylperazine maleate, NF)

Tablets—10 mg (thiethylperazine maleate, NF)

Torecan® (thiethylperazine)
Tablets, Suppositories and Injection

Contraindications: Severe CNS depression, comatose states, and in patients who have demonstrated a hypersensitivity to phenothiazines (e.g., blood dyscrasias, jaundice). Because severe hypotension has been reported after the intravenous administration of phenothiazines, this route of administration is contraindicated. The drug is contraindicated in pregnancy.

Warnings: Phenothiazines are capable of potentiating CNS depressants as well as atropine and phosphorous insecticides. The drug may impair mental and/or physical ability required in the performance of potentially hazardous tasks such as driving a car or operating machinery.

Postoperative Nausea and Vomiting: When used to control postoperative nausea and vomiting in patients undergoing elective surgical procedures, restlessness and postoperative CNS depression during anesthesia recovery may occur. Possible postoperative complications of a severe degree of any of the known reactions of this class of drug must be considered. Postural hypotension may occur after an initial injection, rarely with the tablet or suppository. Do not use with epinephrine in the treatment of drug-induced hypotension as phenothiazines may induce a reversed epinephrine effect. The most suitable vasoconstrictor agents are levarterenol and phenylephrine. The use of Torecan has not been studied following intracardiac and intracranial surgery. Not recommended for use in children under 12 years of age, or in nursing mothers since safety and efficacy have not been established.

Precautions: Convulsions and abnormal movements such as extrapyramidal symptoms have occurred. The varied extrapyramidal symptom complex is more likely to occur in young adults and children. Extrapyramidal effects must be treated by reduction of dosage or cessation of medication. For treatment of nausea and/or vomiting associated with anesthesia and surgery, the drug should be administered by deep intramuscular injection at or shortly before the termination of anesthesia.

Adverse Reactions: CNS: convulsions, extrapyramidal symptoms such as dystonia, torticollis, oculogyric crisis, akathisia and gait disturbances, occasional cases of dizziness, headache, fever and restlessness have been reported. Drowsiness may occur initially on injection but is usually alleviated by a reduction in dosage. Dryness of the mouth and nose, blurred vision, tinnitus; sialorrhea and altered gustatory sensation. Peripheral edema of the arms, hands and face. Cholestatic jaundice; cerebral vascular spasm and trigeminal neuralgia have been reported occasionally. The following have occurred with phenothiazine derivatives and should be considered: agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia, pancytopenia, eosinophilia, leukocytosis; miosis, obstipation, anorexia, paralytic ileus; erythema, exfoliative dermatitis and contact dermatitis; jaundice, biliary stasis. Hypotension, rarely leading to cardiac arrest; ECG changes. Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia, some of which have persisted for several months or years especially in patients of advanced age with brain damage. Menstrual irregularities, altered libido, gynecomastia, weight gain; false positive pregnancy tests. Urinary retention, incontinence; fever, laryngeal edema and angioneurotic edema, asthma. Hyperpyrexia, behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. ECG changes. While there is no evidence that ECG changes are in any way precursors of any significant disturbance of cardiac rhythm, sudden and unexpected deaths apparently due to cardiac arrest have been reported in a few instances in hospitalized psychotic patients previously showing characteristic ECG changes. A peculiar skin-eye syndrome, which is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea, has also been recognized as a side effect following long-term treatment. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported.

Drug Interactions: Phenothiazines are capable of potentiating CNS depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorous insecticides. The drug may induce a reversed epinephrine effect on occasion.

For complete details, please see full prescribing information.

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Ridgefield, CT 06877

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

DAVID C. SABISTON, JR., M.D., *Chairman*
Durham, N. C.

J. WESLEY ALEXANDER, M.D.
Cincinnati, O.

WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.

W. GERALD AUSTEN, M.D.
Boston, Mass.

HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.

WARREN H. COLE, M.D.
Asheville, N. C.

MICHAEL E. DE BAKEY, M.D.
Houston, Tex.

STANELY J. DUDRICK, M.D.
Houston, Tex.

J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.

PAUL A. EBERT, M.D.
San Francisco, Calif.

ERIC W. FONKALSRUD, M.D.
Los Angeles, Calif.

FRANK L. A. GERBODE, M.D.
San Francisco, Calif.

FRANK GLENN, M.D.
New York, N. Y.

FRASER N. GURD, M.D.
Ottawa, Canada

OLGA M. JONASSON, M.D.
Chicago, Ill.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.

LEONARD D. MILLER, M.D.
Philadelphia, Pa.

FRANCIS D. MOORE, M.D.
Boston, Mass.

WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.

JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.

JONATHAN E. RHOADS, M.D.
Philadelphia, Pa.

PAUL S. RUSSELL, M.D.
Boston, Mass.

JOHN A. SCHILLING, M.D.
Seattle, Wash.

G. THOMAS SHIRES, M.D.
New York, N. Y.

HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.

DAVID B. SKINNER, M.D.
Chicago, Ill.

FRANK C. SPENCER, M.D.
New York, N. Y.

SAMUEL A. WELLS, JR., M.D.
Durham, N. C.

Emeritus Members

William F. Rienhoff, Jr., Baltimore, Md.
John D. Stewart, M.D., Boca Raton, Fla.

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Second-class postage paid at Philadelphia, Pa., and at additional mailing offices. Published monthly.
Subscription $26.00 per United States. Resident Rate (U.S. only) $19.00.
All other countries $35.00. Single issue $4.00. All prices include postage.

Copyright © 1978 by J. B. Lippincott Co., East Washington Square, Philadelphia, Pa. 19105. Printed in U.S.A.

Space Age Microbicidal Power

Prep with BETADINE®

Surgical Scrub/Solution/Aerosol Spray

For optimal preoperative skin degerming—BETADINE Surgical Scrub. Chosen by NASA for Apollo 11/12/14 splashdowns, BETADINE Surgical Scrub provides a golden microbicidal lather for prepping the operative site...kills both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, protozoa and yeasts...promptly achieves full microbicidal effect with each usage. (In the rare instance of local irritation or sensitivity, discontinue use in the individual.)

To enhance antisepsis—BETADINE Solution or BETADINE Aerosol Spray. After initial prepping with BETADINE Surgical Scrub, paint the operative area with BETADINE Solution (chosen by NASA for the Skylab mission), or spray with BETADINE Aerosol Spray...both are fully microbicidal and film-forming...maintain microbicidal activity in the presence of blood, pus and serum...treated area may be bandaged, taped or covered by a cast.

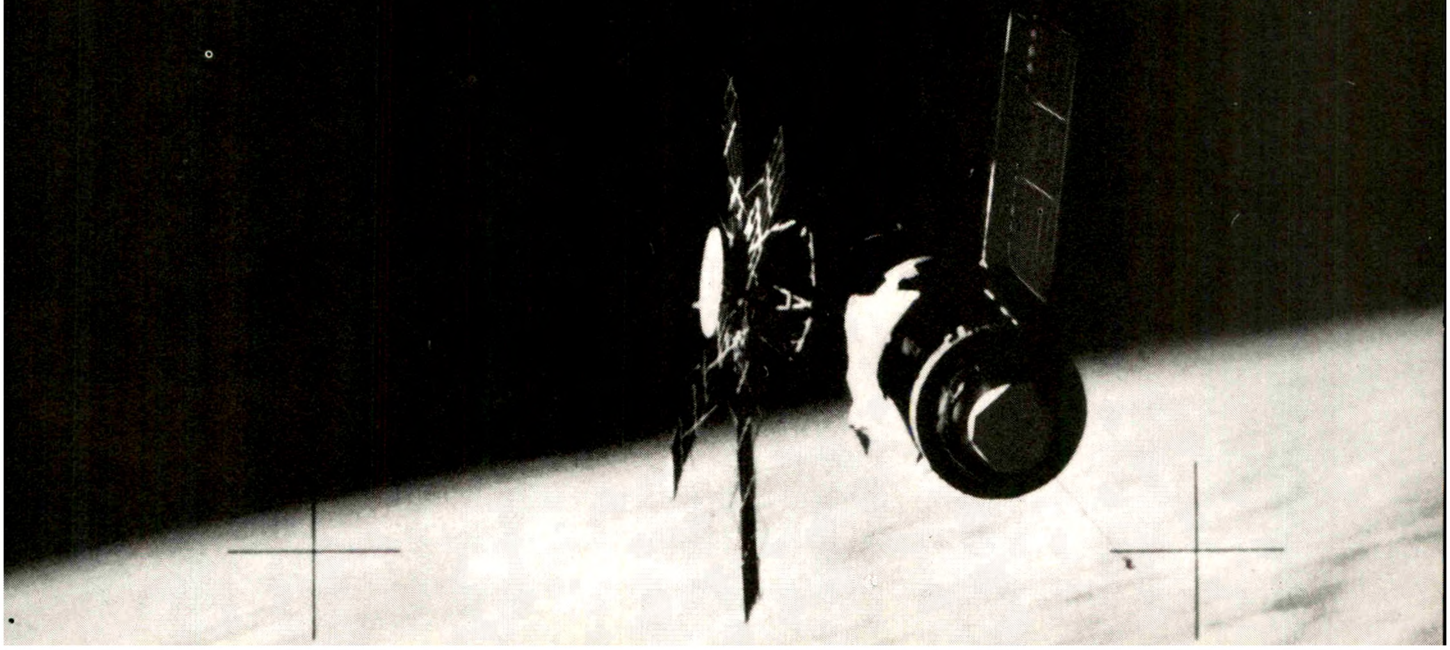
To help maintain postoperative antisepsis—Reapply BETADINE Solution or BETADINE Aerosol Spray after suturing and during redressing. BETADINE microbicides are virtually nonirritating and do not stain skin and natural fabrics.

PHOTOGRAPH: SKYLAB IN ORBIT. COURTESY OF THE NATIONAL AERONAUTICS AND SPACE ADMINISTRATION.

BETADINE
Microbicides
Chosen
by NASA
Apollo
Skylab

Purdue Frederick

©COPYRIGHT 1974, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856 A7475 142074



Bacteroides

may be implicated in a number of clinical situations, including . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena

Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for drugs are ineffective or contraindicated.

But when bacteroides are implicated, Chloromycetin (chloramphenicol) therapy may well be the conservative course. For, in such situations, the benefits-to-risk ratio with Chloromycetin is very favorable.

See next page for full prescribing

Bacteroides...

often an indication for

CHLOROMYCETIN®

(chloramphenicol) Sodium Succinate

PARKE-DAVIS

Prescribing information—Chloromycetin
(chloramphenicol) Sodium Succinate
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae.* It is particularly active against *Salmonella typhi* and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**

   It is not recommended for the routine treatment of the typhoid carrier state.
2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.
   - a) *Salmonella* species
   - b) *H influenzae,* specifically meningeal infections
   - c) Rickettsia
   - d) Lymphogranuloma-psittacosis group
   - e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   - f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
  - (1) abdominal distension with or without emesis;
  - (2) progressive pallid cyanosis;
  - (3) vasomotor collapse, frequently accompanied by irregular respiration;
  - (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off RJ

PD-JA-1280-2-P (2-75)

PARKE, DAVIS & COMPANY, Detroit, Michigan 48232

ANNALS OF SURGERY

Vol. 187 June 1978 No. 6

CONTENTS

583 A Clinical Evaluation of the Surgical Treatment of Anorectal Malformations (Imperforate Anus)
E. Ide Smith, M.D., *William P. Tunell,* M.D., *G. Rainey Williams,* M.D., *Oklahoma City, Oklahoma*

593 Selection of Treatment in the Management of Thyrotoxicosis in Childhood and Adolescence
Arden L. Hothem, M.D., *Colin G. Thomas, Jr.,* M.D., *Judson J. Van Wyk,* M.D., *Chapel Hill, North Carolina*

599 Liver Resection in Children with Hepatic Neoplasms
Judson G. Randolph, M.D., *R. Peter Altman,* M.D., *Robert M. Arensman,* M.D., *Michael E. Matlak,* M.D., *Sanford L. Leiken,* M.D., *Washton, D.C.*

606 Abdominal Drainage Following Appendectomy and Cholecystectomy
H. Harlan Stone, M.D., *C. Ann Hooper,* B.A., B.S., R.N., *William J. Millikan, Jr.,* M.D., *Atlanta, Georgia*

613 Intraperitoneal Povidone-iodine in Experimental Peritonitis
M. Celeste Lagarde, M.D., *John S. Bolton,* M.D., *Isidore Cohn, Jr.,* M.D., *New Orleans, Louisiana*

620 Microsurgical Composite Tissue Transplantation
Donald Serafin, M.D., *Nicholas G. Georgiade,* M.D., *Durham, North Carolina*

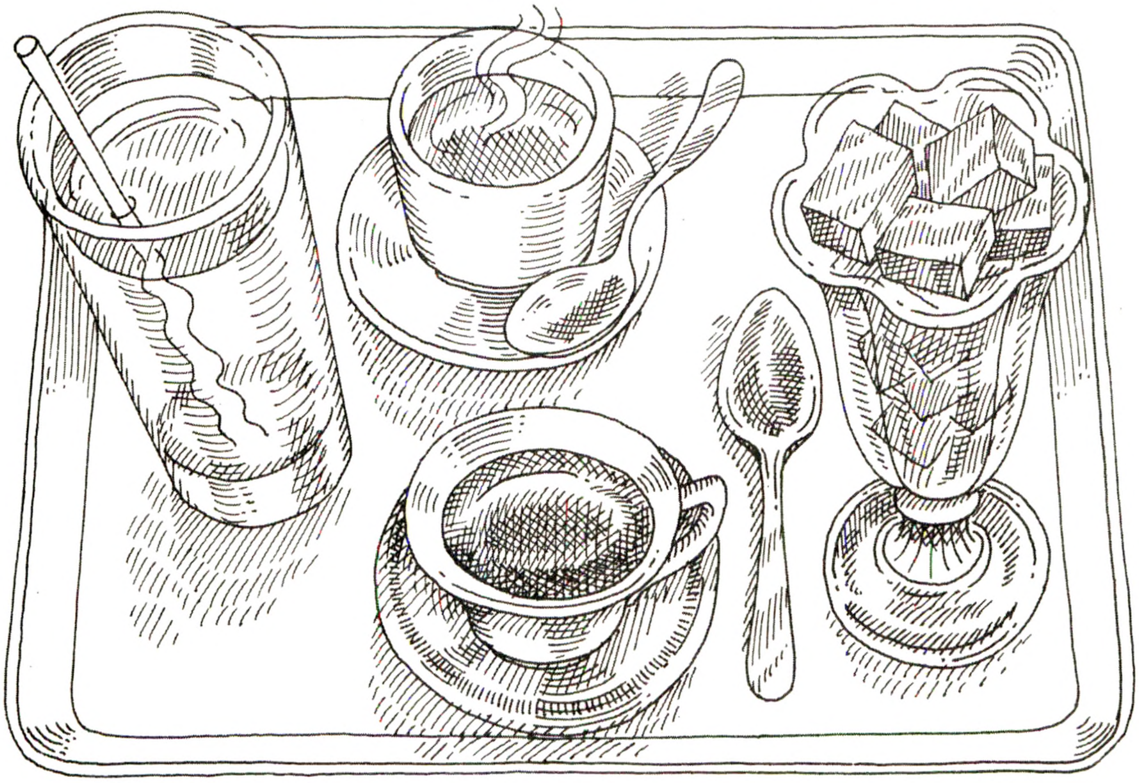
629 Esophageal Resection and Replacement for Carcinoma
E. F. Parker, M.D., *J. F. Ballenger,* M.D., *K. C. Shull,* M.D., *Charleston, South Carolina*

634 Spontaneous Rupture of the Esophagus
Panagiotis N. Symbas, M.D., *Charles R. Hatcher, Jr.,* M.D., *Nickolaos Harlaftis,* M.D., *Atlanta, Georgia*

Continued on p. 12A

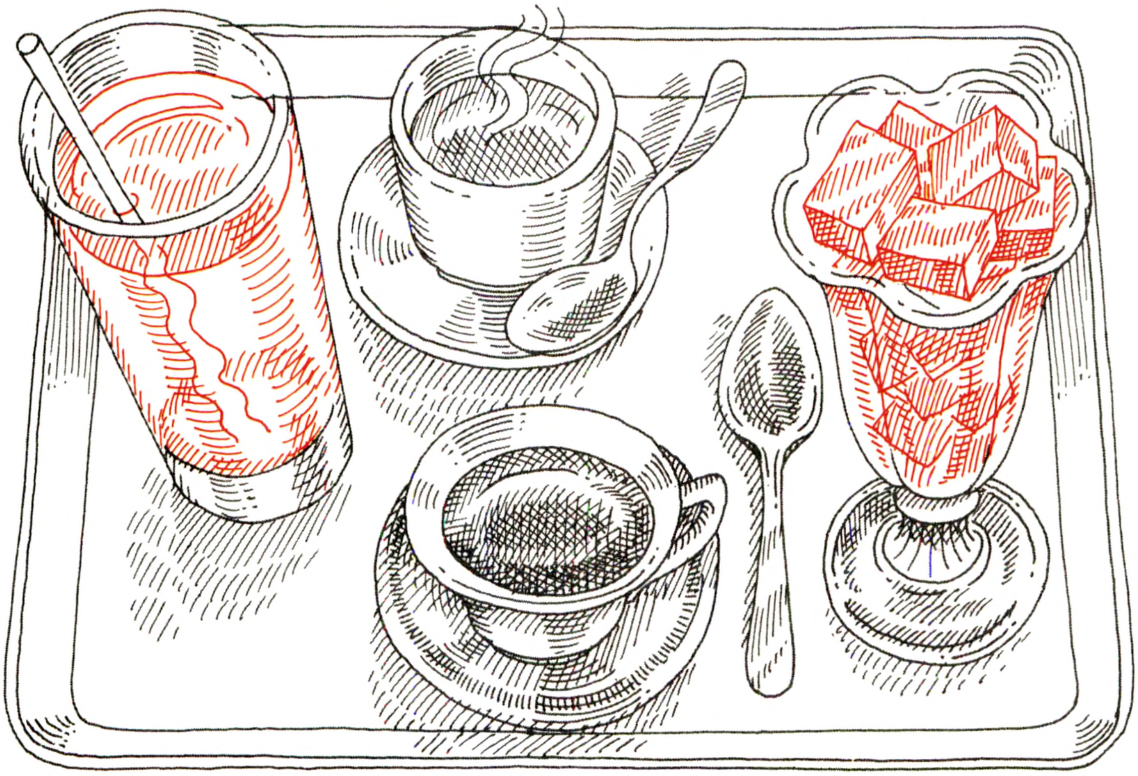
Starvation diet?

Standard clear liquid regimen: 400 kcal daily—trace protein



Not when you fortify with Vivonex® HN!

Clear liquid regimen fortified with 5 packets Vivonex HN:
1,900 kcal, 10 gm nitrogen (62.5 gm protein) daily

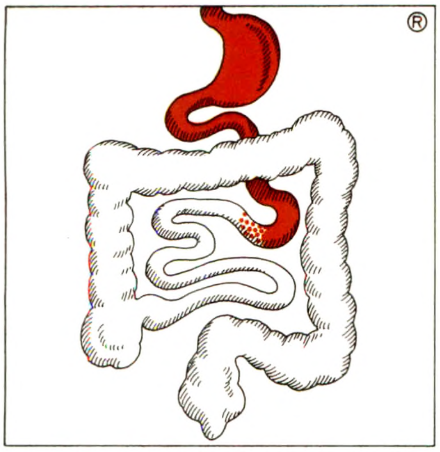


For the nutritional management of protein-calorie malnutrition...Vivonex HN

The usual clear liquid regimen provides only 400 calories daily, with only trace protein. The addition of Vivonex HN to the regimen can add substantial amounts of vital protein and calories for the nutritional management of protein-calorie malnutrition. Vivonex HN is readily accepted by patients on clear liquid regimens when mixed into gelatin desserts, or when served as a beverage in the various flavors now available with Vivonex Flavor Packets.

Because Vivonex HN is formulated with free amino acids, simple carbohydrate and low fat, it requires virtually no active digestion and is absorbed almost completely with negligible residue. Thus it supports the diet objective.

Add Vivonex HN to conventional clear liquids before and after surgery, and when clean-bowel preparation is necessary before surgery or diagnostic procedures. Vivonex HN is also valuable as an enteral alternative to parenteral feeding, as an adjunct to routine parenteral glucose and fluids, and for patients with GI disorders.



Protein-calorie fortification... negligible residue

Vivonex® HN

HIGH
NITROGEN
SOLUBLE
POWDER

free amino acid...complete enteral nutrition minimal digestion...maximal absorption

Supplied unflavored in boxes containing ten 80-gram packets. Each packet provides 300 kcal, 2 gm usable nitrogen (12.5 gm usable protein), as well as carbohydrate, fat, essential vitamins and minerals.

Flavor with Vivonex Flavor Packets
(artificially flavored) Orange, strawberry, grape, beef broth, and tomato. *Also available:* Vivonex Standard Diet. Supplied unflavored in boxes containing six 80-gram packets. Each packet provides 300 kcal. Six packets provide 1,800 kcal, 5.88 gm usable nitrogen (36.75 gm usable protein).

Please note: Information on Vivonex usage and precautions accompanies the product and should be reviewed before use.

® Originators of chemically defined diets
EATON LABORATORIES
division of Morton-Norwich Products, Inc.
Norwich, New York 13815

CONTENTS *Continued*

641 **Inferior Mesenteric Artery Stump Pressure: A Reliable Index for Safe IMA Ligation During Abdominal Aortic Aneurysmectomy**
Calvin B. Ernst, M.D., *Patrick F. Hagihara,* M.D., *Michael E. Daugherty,* M.D., *Ward O. Griffen, Jr.,* M.D., *Lexington, Kentucky*

647 **Extra-anatomic Bypass of the Abdominal Aorta: Management of Postoperative Thrombosis**
Robert W. Oblath, M.D., *Richard M. Green,* M.D., *James A. DeWeese,* M.D., *Charles G. Rob,* M.D., *Rochester, New York*

653 **Vascular Reconstructive Surgery Following Myocardial Revascularization**
William H. Edwards, M.D., *Joseph L. Mulherin, Jr.,* M.D., *William E. Walker,* M.D., PH.D., *Nashville, Tennessee*

658 **Further Evaluation of the Surgical Treatment of Obstructive Disease of the Left Main Coronary Artery**
William C. Alford, Jr., M.D., *Harry L. Page, Jr.,* M.D., *George R. Burrus,* M.D., *Robert A. Frist,* M.D., *William S. Stoney,* M.D., *Clarence S. Thomas, Jr.,* M.D., *William E. Walker,* M.D., PH.D., *Nashville, Tennessee*

665 **Factors Influencing Late Survival After Coronary Bypass Surgery**
Gerald M. Lawrie, M.D., *George C. Morris, Jr.,* M.D., *Houston, Texas*

677 **Subject Index to Volume 187**

683 **Author Index**

Are you at high risk for Hepatitis B?

Now available for post-exposure prophylaxis

H-BIG®

HEPATITIS B IMMUNE GLOBULIN (HUMAN)

from ABBOTT
Scientific Products Division

Provides short-term protection for individuals accidentally exposed to material reactive for HB$_s$Ag by:

- parenteral means (e.g., accidental needle-stick)
- oral means (e.g., pipetting accident)
- direct mucous membrane contact (e.g., accidental splash)

Who's at risk?

- Staff and patients in hemodialysis units, oncology wards
- Operating room personnel
- Technologists in private and hospital laboratories, blood banks
- Physicians—especially surgeons
- Dentists—especially oral surgeons
- Staff and patients in long-term institutions
- Chronic users of injection therapy
- Other hospital staff

ABBOTT Scientific Products Division
Abbott Laboratories
820 Mission Street, South Pasadena, California 91030

Brief Summary

Clinical Pharmacology/Biological Activity: HEPATITIS B IMMUNE GLOBULIN (HUMAN) provides passive immunization for individuals exposed to the hepatitis B virus (HBV) as evidenced by a reduction in the attack rate of hepatitis B following its use. The administration of the usual recommended dose of this immune globulin generally results in a detectable level of circulating anti-HB$_s$ which persists for approximately two months or longer. Cases of type B hepatitis are rarely seen following exposure to HBV in persons with pre-existing anti-HB$_s$. No confirmed instance of transmission of hepatitis B has been associated with this product.

Indications: HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®] is indicated for post-exposure prophylaxis following either parenteral exposure, e.g., by accidental "needle-stick," or direct mucous membrane contact, (e.g., accidental splash), or oral ingestion, (e.g., pipetting accident) involving HB$_s$Ag positive materials such as blood, plasma or serum.

Use of HEPATITIS B IMMUNE GLOBULIN (HUMAN) in other situations has been and continues to be evaluated, but there are not sufficient data at present on effectiveness, dosage and schedule for any other uses to be included as definite indications. There is currently some controversy over whether immune globulin containing a low or a high anti-HB$_s$ titer is preferable in these other situations.

Contraindications: There are no specific contraindications for HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®]. No adverse reactions have been seen in individuals with pre-existing hepatitis B surface antigen although data regarding this occurrence are limited.

Warning: HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®] should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immune globulin preparations.

Precautions: *GENERAL:* HEPATITIS B IMMUNE GLOBULIN (HUMAN) [H-BIG®] should not be administered intravenously because of the potential for serious reactions. Injections should be made intramuscularly, and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel.

CLINICAL AND LABORATORY TESTS: None required.

SPECIAL INSTRUCTIONS: Although systemic reactions to immune globulin preparations are rare, epinephrine should be available.

Clinically Significant Product Interactions: Live virus vaccines such as measles vaccine should not be given close to the time of HEPATITIS B IMMUNE GLOBULIN (HUMAN) administration because antibodies in the globulin preparation may interfere with the immune response to the vaccination.

No interactions with other products are known.

Pregnancy: No studies have been conducted in pregnant patients. Clinical experience with other immunoglobulin preparations administered during pregnancy suggests that there are no known adverse effects on the fetus from immune globulins per se, but there are no reported studies indicating whether or not such adverse effects occur.

Adverse Reactions: Local pain and tenderness at the injection site, and urticaria and angioedema may occur; anaphylactic reactions, although rare, have been reported following the injection of human immune globulin preparations.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Order Today—We have prepared a package of information and a slide presentation to acquaint you and your staff with Hepatitis B Immune Globulin. Return coupon for more information.

Send to: ABBOTT Scientific Products Division
820 Mission Street
South Pasadena, California 91030

☐ Please send informational materials
☐ Contact me to arrange for slide presentation
☐ Send ordering information for H-BIG
☐ Have representative contact me

Name

Position

Institution

Address

City State Zip

AS6

Notice to Contributors and Subscribers

ANNALS OF SURGERY is a monthly journal which considers for publication original articles in the field of surgery. It is the oldest continuously published journal in the English language solely devoted to the surgical sciences. The Editorial Board considers only papers judged to offer significant contributions to the advancement of surgical knowledge.

CONTRIBUTIONS. Four typed copies of the manuscript and four copies of the illustrations should be sent prepaid to the Chairman of the Editorial Board of ANNALS OF SURGERY:

David C. Sabiston, Jr., M.D.
Annals of Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

Manuscripts and references should be typed double spaced on one side of 8½ × 11 paper leaving wide margins. Authors should retain a complete copy of the manuscript including illustrations in the event that the manuscripts are lost in the mail. A complete address for reprint requests should be included on the title page together with the name of the institution from which the work is being published.

An abstract of *not more than 200 words* should be placed at the beginning of the manuscript. It should accurately reflect the paper and provide readers with a reliable impression of the contents and conclusions of the work.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement should be expressed in the metric system. Temperature should be expressed in degrees centigrade. All contributions should be submitted in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Color illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink or transfer lettering, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

An alphabetical list of numbered references should appear at the end of the manuscript with corresponding numbers in the text. All references should be specifically mentioned in the body of the manuscript. The list of references should be *selective* with not more than 20 references except under unusual circumstances. References should conform to the style of the Index Medicus.

McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., 174:58, 1971.

PUBLISHER'S NOTICES

CHANGE OF ADDRESS: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

BUSINESS ADDRESS: Subscriptions, reprints, advertising, and all business communications should be addressed to:

ANNALS OF SURGERY
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $25.00 per year in United States and possessions; all other countries $34.00. All prices include postage. Single issues $4.00. Rate for Residents, U.S. only, $19.00.

The publishers accept no responsibility for opinions expressed by contributors.

When vitamin B-complex with C is indicated

5 ~~4~~ REASONS TO PRESCRIBE BEROCCA® TABLETS

Rx only

Balanced formula **1** High potency B-complex with 500 mg vitamin C tablets for patients such as those with chronic disease, febrile illness or GI disorders, and surgical patients or heavy drinkers.

Better patient compliance **2** The specific instructions accompanying a prescription may encourage patients to adhere to the regimen *you* recommend.

Virtually no odor or aftertaste **3** Eliminates these unpleasant characteristics often associated with B-complex with C products.

Low cost **4** Economically priced; costs no more than many other brands.

Rx only

Rx only guarantees your involvement in *total* patient management. In addition, with Rx only the patient may qualify for third-party reimbursement.

Please see complete product information, a summary of which follows:

Each Berocca Tablet contains:

Thiamine mononitrate (Vitamin B_1)	15 mg
Riboflavin (Vitamin B_2)	15 mg
Pyridoxine HCl (Vitamin B_6)	5 mg
Niacinamide	100 mg
Calcium pantothenate	20 mg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Folic acid	0.5 mg
Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

Dosage: 1 or 2 tablets daily, as indicated by clinical need.

Available: In bottles of 100 and 500.

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

For Professionals Only

pHisoHex effectively reduces skin levels of resident gram-positive bacteria—including staph. With a longer duration of action than any iodophor.

When pHisoHex is used regularly, a bacteriostatic film accumulates and usually won't wash away for days. Rinse thoroughly after use, but not with alcohol.

pHisoHex. Because professional people need a professional wash and scrub.

CLINICAL PHARMACOLOGY: pHisoHex is a bacteriostatic cleansing agent. It cleanses the skin thoroughly and has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use. This antibacterial residue is resistant to removal by many solvents, soaps, and detergents for several days.

pHisoHex has the same slight acidity as normal skin (pH value 5.0 to 6.0).

INDICATIONS AND USAGE: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

CONTRAINDICATIONS: pHisoHex should not be used on burned or denuded skin.

It should not be used as an occlusive dressing, wet pack, or lotion.

It should not be used routinely for prophylactic total body bathing.

It should not be used as a vaginal pack or tampon, or on any mucous membranes.

pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

WARNINGS: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Rapid absorption of hexachlorophene may occur with resultant toxic blood levels, when preparations containing hexachlorophene are applied to skin lesions such as ichthyosis congenita, the dermatitis of Letterer-Siwe's syndrome, or other generalized dermatological conditions. Application to burns has also produced neurotoxicity and death.

pHisoHex SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

Infants have developed dermatitis, irritability, generalized clonic muscular contractions and decerebrate rigidity following application of a 6 per cent hexachlorophene powder. Examination of brainstems of those infants revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3 per cent hexachlorophene. Moreover, a study of histologic sections of premature infants who died of unrelated causes has shown a positive correlation between hexachlorophene baths and lesions in white matter of brains.

pHisoHex is intended for **external use only.** If swallowed, pHisoHex is harmful, especially to infants and children. **pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.**

PRECAUTION: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly with water.

ADVERSE REACTIONS: Adverse reactions to pHisoHex may include dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

TREATMENT OF ACCIDENTAL INGESTION: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities.

If patients are seen early, the stomach should be evacuated by emesis or gastric lavage. Olive oil or vegetable oil (60 ml or 2 fl oz) may then be given to delay absorption of hexachlorophene, followed by a saline cathartic to hasten removal. Treatment is symptomatic and supportive; intravenous fluids (5% dextrose in physiologic saline solution) may be given for dehydration. Any other electrolyte derangement should be corrected. If marked hypotension occurs, vasopressor therapy is indicated. Use of opiates may be considered if gastrointestinal symptoms (cramping, diarrhea) are severe. Scheduled medical or surgical procedures should be postponed until the patient's condition has been evaluated and stabilized.

HOW SUPPLIED: pHisoHex is available in unbreakable plastic squeeze bottles of 5 oz (refillable) and 1 pt, and in plastic bottles of 1 gal.

Also available—¼ oz (8 ml) unit packets, boxes of 50.

pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts. A special type of stainless steel must be used or undesirable discoloration of the product or oxidation of metal may occur. Specially designed dispensers for hospital or office use may be obtained through your local dealer.

pHisoHex®
brand of
hexachlorophene detergent cleanser

contains a colloidal dispersion of hexachlorophene 3% (w/w) in a stable emulsion consisting of entsufon sodium, petrolatum, lanolin cholesterols, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH is adjusted with hydrochloric acid. Entsufon sodium is a synthetic detergent (sodium octylphenoxyethoxyethyl ether sufonate).

Winthrop Winthrop Laboratories, New York, NY 10016 3084

ANNALS OF SURGERY

Vol. 187 June 1978 No. 6

A Clinical Evaluation of the Surgical Treatment of Anorectal Malformations (Imperforate Anus)

E. IDE SMITH, M.D., WILLIAM P. TUNELL, M.D. AND G. RAINEY WILLIAMS, M.D.

From the Department of Surgery of the Oklahoma University School of Medicine and the Section of Pediatric Surgery, Oklahoma Children's Memorial Hospital, Oklahoma City, Oklahoma

The surgical correction of anorectal malformations remains a serious problem despite their relatively frequent occurrence. Our surgical experience with 90 patients, seen in the past ten years, includes abdominal-perineal or sacro-abdominal-perineal repair in 28 patients, complete perineal anoplasty in 13 patients, and "cut-back" perineal anoplasty in 38 patients. Secondary surgical procedures for "fecal reservoir syndrome" (seven patients), revision for stricture (11 patients) and excision of redundant mucous membrane (ten patients). The observations made from this clinical study are: 1) The importance of thorough urological and neurological evaluation of "high" abnormalities and the value of the cremasteric and bulbocavernosus reflexes as indicators of sacral innervation. 2) Increasing satisfaction with the "cut-back" anoplasty as a definitive procedure or as a temporary stage in low recto-vaginal or recto-vestibular fistulas. The technique for the "cut-back" is improved by the use of Burow's triangles and the use of nonabsorbable sutures. 3) The advisability of the complete perineal anoplasty with posterior positioning of the anus and construction of a perineal body in patients with low recto-vaginal and recto-vestibular fistulas. 4) A concern over the functional capacity of the distal bowel segment in high abnormalities. This is emphasized by the experience with six secondary resections of the rectosigmoid or left colon for "fecal reservoir syndrome." 5) Heartening results with secondary operations for stricture and redundant mucous membrane which suggest the desirability of an earlier surgical approach to these complications.

THE SURGICAL CORRECTION of anorectal malformations remains a serious and unresolved problem, despite its relatively frequent occurrence. The work of Stephens[21] and others[2,7] has added to an understanding of the embryology and the pathological anatomy of the various types of anorectal malformations. Division of the abnormalities into high (rectal) malformations and into low (anal) malformations[16] has proved to have both therapeutic and prognostic significance.[9,13] Stephens has also clarified the relative importance of the external and internal anal sphincters and of the levator muscular sling, and has demonstrated in high lesions requiring pull-through procedures that bowel control is dependent upon proper functioning of the levator ani muscle. This has led to the preference for sacro-abdomino-perineal approach to the definitive repair of most rectal anomalies. Despite these advances, the primary goal of the surgeon to achieve a repair which provides a nearly normal anal outlet for the patient remains a very evasive one.

Controversy exists over the best management of the baby with a low anovaginal fistula or an anovestibular fistula. Stephens and Smith[21] believe that a "cut-back" anoplasty with the creation of a "shotgun perineum" usually provides the patient with adequate bowel control and genital function. Other pediatric surgeons[8,13,15,17] advocate a mobilization of the distal anorectum and its transplantation posteriorly with the creation of a perineal body—the perineal transplant anoplasty.

Relatively little has been written concerning the management of postoperative complications of anoplasties, although most authors mention problems with post-

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Supported in part by a grant (RR-62) from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

Reprint Requests: E. Ide Smith, M.D., OCMH, Pediatric Surgery, P.O. Box 26307, Oklahoma City, Oklahoma 73126.

Submitted for publication: December 8, 1977.

0003-4932-78-0600-0583-0105 © J. B. Lippincott Company

TABLE 1. *Anorectal Malformations (OCMH 1967–77)*

	Male		Female	
Rectal (High)	Rectourethral fistula	15	Rectocloacal or rectovaginal fistula	10
	Anorectal atresia	3	Rectovesicle fistula	1
	Rectovesicle fistula	2	Cloacal exstrophy	3
	Rectal atresia (Type IV)	1		
	Unknown	7		14 (2 deaths)
		28 (9 deaths)		
Low (Anal)	Anoperineal fistula	16	Anovestibular fistula	24
	Covered anus	1	Anoperineal fistula	5
	Anal stenosis	1	Unknown	1
		18		30 (3 deaths)

operative stricture formation, with excessive mucous membrane following pull-through procedures, and with dilatation of the distal rectosigmoid with the development of megacolon.[3,4]

We have reviewed our clinical experience with 90 patients with anorectal malformations seen in this hospital between 1966 and 1977 in the light of the above problems. Our conclusions represent personal clinical evaluations, and are not intended to provide statistical analysis of the abnormalities nor of the procedures which were employed. Long-term analysis must take into account longer growth and development of the patients, and must be on a five to 15 year basis at least.[9,13,22]

Clinical Data

Ninety patients with anorectal malformation have been treated at the Oklahoma Children's Memorial Hospital from 1966–1977 (Table 1). Forty-eight patients had anal malformations, and 42 patients had rectal abnormalities. The patients ranged in age from the neonatal period to ten years when first seen. Eight patients with anoperineal fistulas were not diagnosed at the time of birth, and presented with obstipation at two months to six years of age.

There were 14 deaths in the total group; eight in the neonatal period and six from 30 days to one year. Concomitant abnormalities, principally congenital heart disease, and necrotizing enterocolitis were the major causes of death.

TABLE 2. *Anorectal Malformations (OCMH 1967–77)*

Primary Treatment Low Malformations	Male	Female	Primary Treatment High Malformations	Male	Female
Cut-back anoplasty	14	20	Colostomy	23	8
			Cut-back	—	2
Colostomy	2	3	Early death	5	—
Perineal transplant	—	4	Perineal anoplasty	—	1
Dilatation	1	2	No Rx	—	1
Other	1	—	Ileostomy	—	2

The usual therapeutic approach in this institution has been the performance of a colostomy in *all* infants with high anomalies in the neonatal period followed by sacro-abdomino-perineal anoplasty at eight to 15 months of age. Anal anomalies with anoperineal fistulae in both sexes are treated definitively with a "cut-back" anoplasty as newborns. Anovestibular or anovulvar fistulas in the female were treated by neonatal perineal transplant and are now treated by a "cut-back" anoplasty as a newborn followed by perineal transplant at eight to 15 months. The operations performed in this series are listed in Tables 2 and 3. With the exception of one neonate who died with gram negative sepsis 24 hours following colostomy, there were no operative or early postoperative deaths.

Noteworthy is one 17-year-old girl who had several attempts at anoplasty during infancy, and has had a colostomy throughout childhood. This patient has made a very successful adjustment and has made a choice for a permanent colostomy. We concur that this patient's potential is better realized with her colostomy. Comparing the "state of the art" for the colostomy patient and for the high anoplasty patient, one is struck by the investment demanded of patient and parents by the latter for the returns received.

The development of secondary complications such as postoperative strictures and the presence of excessive mucous membrane leading to bleeding and skin irritation has been distressingly frequent in our patients. Routine postoperative dilatations have been carried out, but frequent and regular postoperative visits present significant problems to parents in a predominantly rural population. An attempt is made postoperatively to maintain a lumen which accepts a #12 Hegar dilator or the little finger of the parent.

TABLE 3. *Anorectal Malformations (OCMH 1967–77)*

Secondary Definitive Therapy Low Malformation	Male	Female	Secondary Definitive Therapy High Malformation	Male	Female
Cut-back	3	1	Sacro-abdomino-perineal	14	8
Perineal transplant anoplasty	1	8	Abdomino-perineal	1	—
Sacro-perineal	1	1	Sacro-perineal	1	—
Sacro-abdominal-perineal	—	1	Colostomy	—	1
Abdomino-perineal	—	1	No definitive procedure	12	5

We found dilatation by parents at home or by the local physician generally unsatisfactory. Dilatation of established strictures has been uniformly unsuccessful.

The presence of excessive mucous membrane was often seen after pull-through anoplasties, often resulting from concern on the surgeon's part to avoid tension on the anastomosis and to mobilize adequate bowel to prevent disruption. Often excessive mucosa is present with a stricture. The procedures for revision of anoplasty are shown in Table 4.

Although many of our patients are young, and evaluation for bowel and urinary continence is limited, the authors have attempted personally to interview and to examine the evaluable patients in this series. The results of the treatment of the anorectal abnormalities are evaluated in Tables 5–9. The criteria used for classification of bowel function are modified from Kiesewetter:[9] *Good control*: Normal bowel function; soiling absent or very rare; patient may require occasional enema, cathartic or stool softener; no social limitation. *Fair control*: Able to attend school; limited social restriction; soiling occasional to frequent particularly with loose stools, frequent use of enemas, cathartics or stool softeners. *Poor control*: Soiling is social problem; requires pad or diaper; constant soiling often with megacolon; constant use to dependency upon enemas, cathartics and stool softeners.

In some younger children with low abnormalities, we have felt that they were evaluable when toilet-trained at an approximately normal time.

With one exception, all of the patients with abnormal bladder control had either spinal abnormalities or an intrinsic urinary abnormality. The only exception was a male patient who was found to have a neurogenic bladder following a secondary pull-through procedure for "terminal reservoir" syndrome.

Discussion

In any clinical evaluation of pediatric patients following anorectal surgery, the importance of improvement with further growth and development should be considered. Kiesewetter and Chang[9] have stressed the importance of the fact that "continence is more slowly achieved (in the anoplasty patient) than in the normal child." They found that the development of control is an evolutionary process which seems to improve with age up to puberty. It is also apparent that the development of bowel control is not totally a factor of the physical integrity or the strength of the sphincter muscles or the perineal sensation. The importance of parental assistance in training and of the patient's desire, cooperation, and mental ability all seem to play a role in the level of success which a postoperative anoplasty patient achieves. Several patients with a very lax sphincter have achieved good bowel control and rehabilitation. Development of control in a retarded child, on the other hand, poses a formidable challenge regardless of the operative procedure.

Value of Preoperative Evaluation

In planning for the management of the infant or child with anorectal malformation we have learned that identification of the exact type of abnormality is critical (Table 10).[16,18] While complete clarification may not be possible in the neonatal period particularly in rectal anomalies, further studies are possible after the performance of a colostomy and before definitive operation.

In low abnormalities with a fistula, the most valuable examination is palpation through the fistula with a probe or curved clamp to determine the position of the anal pouch. A Foley catheter with markings can be used to determine the length of the fistula.[21] The

TABLE 4. *Procedures for Treatment Complications*

	High		Low	
	Male	Female	Male	Female
Revision anoplasty (stricture—excess mucosa)	11 (18)*	6 (8)*	—	4 (6)*
Colostomy	1	—	—	—
Colon Resection (Reservoir Syndrome)	2	1	2	1
Levatorplasty	—	—	—	1

* Number patients (number procedures).

TABLE 5. *Clinical Evaluation Female Anoplasty Patients (Low)*

				Anoplasty			Sphincters				Control	
Patient	Age (Yr.)	Procedure	Abdominal Exam	Location	Mucosa	Lumen	Ext.	Int.	Lev.	Reflexes	Bowel	Bladder
2	1	CB	—	—	—	—	—	—	—	—	NE	—
3	4	CB	—	—	—	—	—	—	—	—	NE	—
4	9	CB	N	N	N	N	Good	0	Good	?	Good	ABN
11	9/12	CB	—	—	—	—	—	—	—	—	NE	—
15	2	CB	—	—	—	—	—	—	—	—	NE	—
27	3	CB	N	N	N	N	Good	Good	Good	P	Good	N
29	4	CB	N	N	N	N	Poor	Poor	Poor	?	Fair	N
39	4	CB	Megacolon	Ant.	N	N	Poor	Fair	Good	0	Poor	N
40	6	CB	—	—	—	—	—	—	—	—	NE	—
43	7	CB	N	N	N	N	Good	Good	Good	?	Good	N
44	7	CB	—	—	—	—	—	—	—	—	NE	—
12	1½	CB-PT	Megacolon	—	—	—	—	—	—	—	NE	—
14	3	CB-PT	N	N	N	Stric.	—	—	—	—	NE	—
16	7	CB-PT	N	N	N	N	Fair	Fair	Good	?	Good	N
17	2½	CB-PT	N	N	N	N	Fair	0	Fair	P	Fair	ABN
32	7	CB-PT	N	N	N	N	Fair	Fair	Fair	?	Poor	N
35	1½	CB-PT	N	N	N	N	Fair	0	Fair	P	NE	N
41	1½	DIL-CB	N	N	N	N	Good	Good	Good	—	NE	—
1	8	PT	Megacolon	N	N	N	Fair	0	Fair	P	Fair	N
10	8	PT	N	N	N	N	Good	Good	Good	P	Good	N
26	8	PT	N	N	N	N	Fair	0	Fair	P	Fair	N
38	5	COL-CB	N	Ant.	N	N	Good	Good	Good	P	Good	N
6	5	COL-PT	N	N	N	N	Good	Good	Good	?	Good	N
37	11	COL-PT	N	N	N	N	Good	Good	Good	?	Good	N
8	12	DIL-SP	Megacolon	N	Xs	Lax	Fair	Poor	Fair	P	Fair	N
23	16	PT-ASP	0	N	N	N	0	0	Fair	0	Good	N
47	11	COL-AP	N	N	N	N	Good	Good	Good	P	Good	N

N = Normal, NE = Not Evaluable, ABN = Abnormal, P = Present, 0 = Absent, Ant. = Anterior, Post. = Posterior, Lat. = Lateral, Xs = Excess mucous membrane, Stric. = Stricture, CB = Cut-back anoplasty. DIL = Dilatation, PT = Perineal transplant anoplasty, COL = Colostomy, ASP = Abdomino-sacro-perineal anoplasty, AP = Abdomino-perineal anoplasty, SP = Sacro-perineal anoplasty.

TABLE 6. *Clinical Evaluation Male Anoplasty Patients (Low)*

				Anoplasty			Sphincters				Control	
Patient	Age (Yr.)	Procedure	Abdominal Exam	Location	Mucosa	Lumen	Ext.	Int.	Lev.	Reflexes	Bowel	Bladder
7	2	CB	N	N	N	N	—	—	—	—	NE	—
9	1½	CB	—	—	—	—	—	—	—	—	NE	—
13	8/12	CB	—	—	—	—	—	—	—	—	NE	—
18	1½	CB	N	N	Xs	Stric.	Fair	0	0	0	Good	N
19	1½	CB	N	N	N	N	Good	Good	Good	?	Good	N
20	4	CB	N	Ant	N	N	Fair	Good	Good	?	Good	N
21	1	CB	N	N	N	N	Good	Good	Good	N	Good	N
22	8	CB	N	N	N	N	Fair	Fair	Good	N	Good	N
25	4	CB	—	—	—	—	—	—	—	—	NE	—
30	1½	CB	N	N	N	N	—	—	—	—	NE	—
31	12	CB	ABN	N	N	N	Good	Good	Good	N	Fair	N
33	3	CB	N	N	Xs	N	Fair	0	Good	N	Fair	N
34	7/12	CB	N	N	N	N	Good	Good	Good	N	Good	N
36	8	CB	N	N	N	N	Good	Good	Good	N	Good	N
42	2	CB	N	Ant	N	N	Fair	Good	Good	N	Good	N
46	8	CB	N	N	N	Lax	0	0	Fair	N	Poor	ABN
47	6	CB	N	N	N	N	Fair	—	—	?	NE	—

N = Normal, NE = Not Evaluable, ABN = Abnormal, P = Present, 0 = Absent, Ant. = Anterior, Post. = Posterior, Lat. = Lateral, Xs = Excess mucous membrane, Stric. = Stricture, CB = Cut-back anoplasty, DIL = Dilatation, PT = Perineal transplant anoplasty, COL = Colostomy, ASP = Abdomino-sacro-perineal anoplasty, AP = Abdomino-perineal anoplasty, SP = Sacro-perineal anoplasty.

TABLE 7. *Clinical Evaluation Female Anoplasty Patients (High)*

				Anoplasty			Sphincters				Control	
Patient	Age (Yr.)	Procedure	Abdominal Exam	Location	Mucosa	Lumen	Ext.	Int.	Lev.	Reflexes	Bowel	Bladder
e	1½	COL-ASP	N	N	N	Stric.	—	—	—	—	NE	—
i	9	ASP	—	—	—	—	—	—	—	—	NE	—
m	3	COL-ASP	N	N	Xs	Stric.	Poor	0	Good	N	Fair	N
p	8	COL-ASP	N	Ant.	N	Stric.	0	0	Poor	?	Poor	N
v	6	COL-ASP	N	Post.	N	Stric.	0	0	Poor	Right Only	Poor	ABN
x	4	COL-ASP	N	Ant-Lat	Xs	N	0	0	Fair	0	Poor	ABN
ee	2	COL-ASP	—	—	—	—	—	—	—	—	NE	—
gg	7	COL-ASP	N	N	N	Stric.	Poor	0	Fair	?	Fair	N

N = Normal, NE = Not Evaluable, ABN = Abnormal, P = Present, 0 = Absent, Ant. = Anterior, Post. = Posterior, Lat. = Lateral, Xs = Excess mucous membrane, Stric. = Stricture, CB = Cut-back anoplasty, DIL = Dilatation, PT = Perineal transplant anoplasty, COL = Colostomy, ASP = Abdomino-sacro-perineal anoplasty, AP = Abdomino-perineal anoplasty, SP = Sacro-perineal anoplasty.

most difficult problems in our experience have been the recto-vestibular fistula which presents in similar fashion to the common anovestibular fistula, and the recto-bulbar fistula in the male.

Preoperative assessment of the nerve supply to the anal area, the sphincter, and the levator muscle is vitally important for future continence. Congenital absence or dysfunction of the sacral plexus is usually reflected in bladder dysfunction. Although difficult to determine in the neonate, bladder function remains an important indicator of the presence or absence of normal anal sphincters and the levator sling. The presence of perineal reflexes including the cremasteric for lumbar function and the bulbocavernosus for sacral function are invaluable aids in demonstrating the presence of intact perineal sensation and possible motor function. We have begun to use the bulbocavernosus stimulation of the anal muscles as a preoperative and postoperative test of nerve integrity following pelvic operations. Sacral agenesis, or abnormalities of S2, S3, S4 all should raise concern for the integrity of the sphincter mechanism.

In planning any operative procedure, including colostomy, a foreknowledge of other possible abdominal procedures is helpful. This depends on thorough evaluation of the urinary and genital tracts as well as the remaining gastrointestinal tract. Anorectal manometry was not available for the study of these

TABLE 8. *Clinical Evaluation Male Anoplasty Patients (High)*

				Anoplasty			Sphincters				Control	
Patient	Age (Yr.)	Procedure	Abdominal Exam	Location	Mucosa	Lumen	Ext.	Int.	Lev.	Reflexes	Bowel	Bladder
f	4	COL-ASP	N	N	N	N	Fair	0	Good	N	Poor	N
g	3	COL-ASP	N	N	N	N	0	0	Good	N	Poor	ABN
h	4	COL-ASP	N	N	N	Stric.	0	0	Good	?	Poor	N
j	7	COL-ASP	—	—	—	—	—	—	—	—	NE	—
k	5	COL-ASP	N	N	N	N	Poor	0	Good	N	Fair	N
q	5	COL-ASP	N	N	N	N	Fair	Fair	Good	?	Poor	ABN
s	4	COL-ASP	N	Lat	Xs	N	0	0	Fair	?	Poor	ABN
u	7	COL-ASP	N	N	N	N	Poor	0	Fair	?	Fair	N
w	6	COL-ASP	N	N	Xs	N	0	0	Poor	?	Poor	N
aa	6	COL-ASP	N	N	N	Stric.	Poor	?	?	N	Fair	N
bb	1½	COL-AP	—	—	—	—	—	—	—	—	NE	—
hh	5	COL-ASP	N	Post	Xs	Stric.	0	0	Fair	N	Poor	N
ii	3	COL-ASP	N	N	N	Stric.	0	0	Fair	?	Poor	N
jj	1½	COL-ASP	—	—	—	—	—	—	—	—	NE	—
mm	2	COL-SP	N	N	N	N	Good	Fair	Good	N	Good	N
oo	6	COL-ASP	N	N	N	Stric.	Fair	0	Fair	N	Poor	N

N = Normal, NE = Not Evaluable, ABN = Abnormal, P = Present, 0 = Absent, Ant. = Anterior, Post. = Posterior, Lat. = Lateral, Xs = Excess mucous membrane, Stric. = Stricture, CB = Cut-back anoplasty, DIL = Dilatation, PT = Perineal transplant anoplasty, COL = Colostomy, ASP = Abdomino-sacro-perineal anoplasty, AP = Abdomino-perineal anoplasty, SP = Sacro-perineal anoplasty.

TABLE 9. *Results of Treatment*

	High		Low	
	Male	Female	Male	Female
Good	1	—	8	10
Fair	3	2	2	5
Poor	9	3	1	2
NE	3	3	6	10

patients, but we believe will prove to be a valuable adjunct in the pre and postoperative assessment of these patients.[1]

Value of the Cut-Back Anoplasty as Both a Primary and Definitive Procedure

The cut-back anoplasty as first popularized by Browne[6] is a simple incision with scissors of an anoperineal or anovestibular fistula posteriorly to the area of the external anal sphincter. This has been employed as a primary and definitive procedure for males with perineal fistulas and for females with both perineal and vestibular or vulvar fistulas. Our use of this procedure is summarized in Tables 5 and 6. These results show a predictably good result in patients with anoperineal fistulas in both sexes. Recently we have used the cut-back anoplasty as the initial procedure in the female infant with an anovaginal or anovestibular fistula; followed by the definitive perineal transplant anoplasty later. The cut-back anoplasty provides an early and adequate outlet for stool and prevents colonic obstruction and hypertrophy. In evaluation of patients following the cut-back for anoperineal fistulas, there appears to us to be a good external anal sphincter as well as a functioning internal sphincter and levator muscle. The vast majority of these children can be toilet-trained at a normal age, and the end results are the most satisfactory in this whole series.

Our technique of cut-back has undergone several modifications from that originally described. We first used a Y-V plasty with approximation of the unmobilized skin to the mucous membrane. More recently we have added excision of small triangles of skin as shown in Figure 1 (Burow's triangles)[11] a procedure which was first suggested by Dr. Roy Forsyth, one of our residents. The use of these triangles allows the development of a moderate skin flap which advances very well into the mucosal defect; and we have found good healing. Silk or other nonabsorbable suture is used, and is left in for at least 14 days. The use of catgut seemed to result in more wound disruption with a functioning anus; and the use of polyglycolic acid sutures was followed by hypertrophic mounds of skin at the site of the sutures.

Perineal Transplant Anoplasty-Indicated or Not

Our personal preference has been for the performance of a perineal transplant anoplasty. Follow-up studies by Kiesewetter[9] five to 30 years postoperative show good control in 22 transplant anoplasty patients of a total of 24. Smith and Gross[19] found good continence in 116 of 145 patients with low abnormalities after perineal transplant. We have also seen two adult patients who had perineal transplant performed as young adults and both women expressed a strong preference for the posterior location of the anal opening and indicated considerable satisfaction with improved anal continence. Niloff[12] has reported on a similar repair of a patient in adult life with improvement.

The results from perineal transplantation seen in this series, although satisfactory, do not strongly support this viewpoint (Table 5). The external anal sphincter and levator muscle in these patients were often not as strong as might be hoped, though this may reflect the younger age at the time of evaluation. We would still feel, however, that the normal posterior location of the anal orifice separated from the genital tract is important. Vaginal delivery was successfully used in ten adult female patients in the perineal transplant patients studied by Smith and Gross.[19]

"Terminal Reservoir Syndrome"

While Hirschsprung's Disease has been reported with anorectal malformations[14] the development of a dilated segment of the rectosigmoid with normal ganglion cells is seen frequently in both high and low groups, and has variously been called "fecal reservoir syndrome," "terminal reservoir syndrome" and more recently "primary rectal ectasia."[5] The authors distinguish between a megarectum in which secondary hypertrophy may develop in response to anal obstruction, and a condition in which the rectosigmoid is enlarged at birth and remains flaccid and dilated. Their interpretation is that the latter type of flaccid enlargement is inherent to the bowel and this is "primary rectal ectasia." The dilation of the rectosigmoid is usually quite well defined and ends abruptly. It

TABLE 10. *Preoperative Assessment*

- Clinical and radiological identification of type
  - Presence of fistula
  - Relation of levator sling
  - Cystourethrogram or equivalent
- Integrity and function of sphincters and their nerve supply
  - Bladder function
  - Perineal sensation
- Investigation for other abnormalities (including distal rectosigmoid)

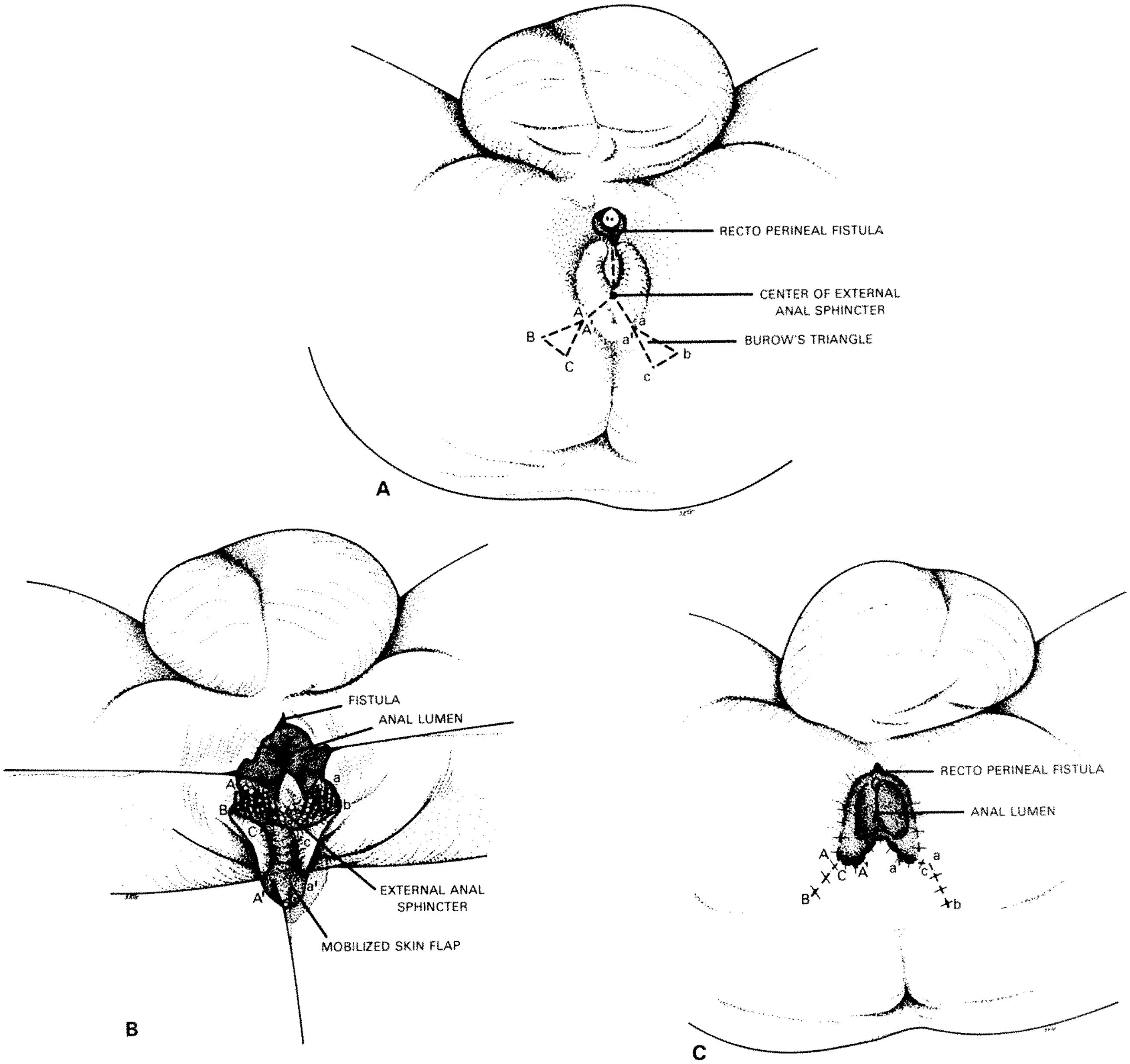


FIG. 1. Technique of cut-back anoplasty using Burow's triangles. (A) An incision is made from the perineal fistula opening to point in the center of external anal sphincter demonstrated by nerve stimulator. Skin flap marked with triangles to be excised. (B) Skin flap developed and small triangles of skin removed. Anal sphincter protected. (C) Closure carried out with fine silk sutures with resultant flap of skin into the posterior mucosal defect.

may be the result of an intrinsic defect in the bowel or its nerve supply or secondary to operative trauma. Such dilatation seen in the five to ten-year-old postoperative anoplasty patient represents a serious and permanent disability. We have seen two patients in whom diverting colostomies were performed and in whom after six months of exclusion there was no regression in the size of bowel nor improvement in function. An additional patient from this series had a flaccid saccular rectosigmoid terminal reservoir thirteen years after a diverting colostomy had been performed. A total of six patients underwent resections of the rectosigmoid with abdomino-perineal pull-through for terminal reservoir syndrome after attempts had been made to manage these patients conservatively with enemas, suppositories and wash-outs (Fig. 2). The ages at the time of resection were one and one-half to 15 years. In all instances there has been a marked improvement in the growth and development of the children and in the avoidance of what had been totally disabling fecal impactions. An additional child had only a full-thickness rectal biopsy.

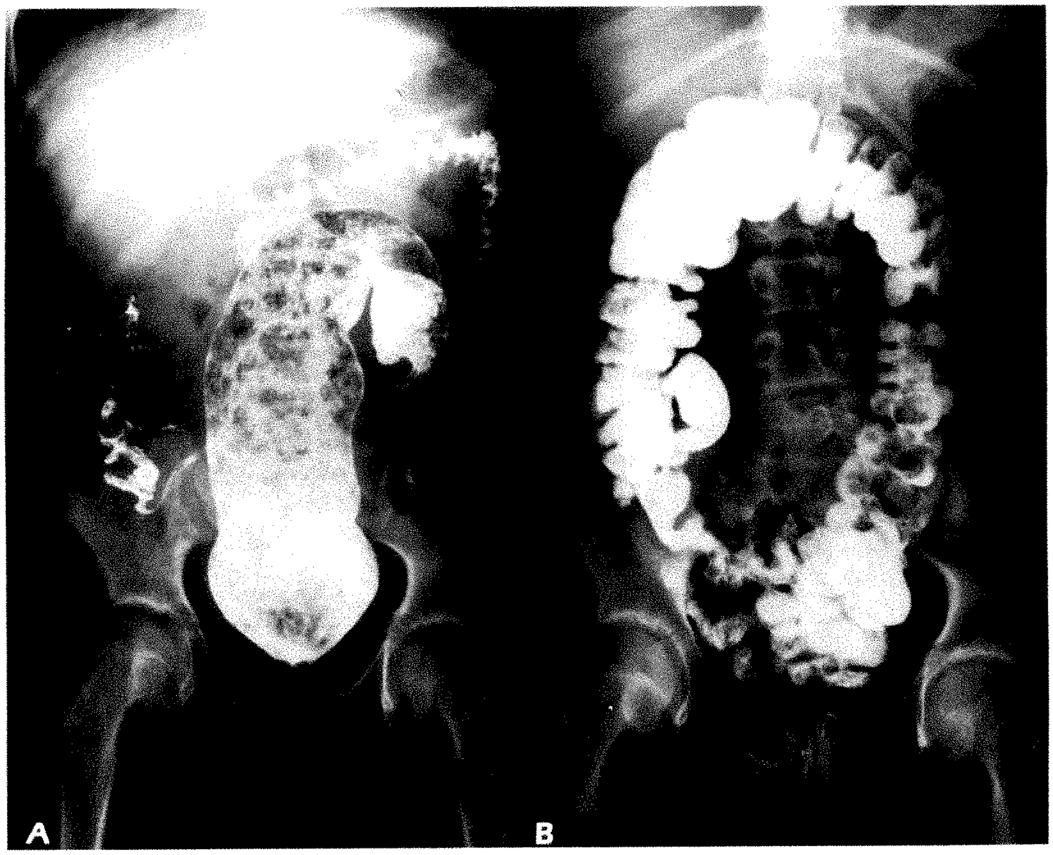


FIG. 2. Preoperative (A) and (B) postoperative radiographic studies of a ten-year-old female with terminal reservoir syndrome treated with rectosigmoid resection and pull-through.

Secondary Complications of Anoplasty

The goal of a cosmetically satisfactory anal opening as well as one which functions normally depends primarily on the operative technique. Although various techniques have been advised for the anastomosis of bowel to the skin of the perineum, problems with strictures and with redundant mucous membrane persist as demonstrated in Table 4. We have been impressed by the healing of anastomoses which were protected by colostomies, and although this represents an additional procedure, greater consideration of this may be in order. The more meticulous management of the ano-cutaneous anastomosis with the use of permanent sutures may also lead to better cosmetic and functional results.

Postoperative dilatation of an anoplasty remains an important adjunct to a successful result. Sommerschild[20] recommends daily dilatation for two years. We believe that the emphasis on dilatation is not misplaced and would attribute some of our poor results to inadequate postoperative dilatation. Our usual goal has been a lumen which will take a #12 Hegar dilator, but this may indeed be too small for other than the neonate, and a size 13–15 may be more appropriate. The development of normal size stools of a normal consistency are helpful. When strictures occur, our experience would suggest that operative correction is desirable where daily dilatation of the strictured area is not successful promptly. It is important to note that the stricture may be in the area of the levator sling. Stephens[21] has stressed the importance of delicate dilatation of the levator sling and with the caution that more vigorous dilatation of this sling may result in fibrosis which is counter-productive.

On the operative approach to correction of stricture, our management at the present time is a posterior Y-V plasty with the use of Burow's triangles, as used in cut-back anoplasty.

Prolapse of excessive mucous membrane or the presence of excessive mucous membrane following anoplasty occurred in a number of our patients. This was often watched with the hope of improvement. We found that this usually does not improve with growth of the patient. The early excision of this tissue, particularly when it is circumferential and protrudes more than 5 mm does appear to add to the bowel control of the patient. Correction also eliminates the frequent bleeding and skin irritation that occurs from excessive mucous membrane. A Whitehead type of amputation of the excessive mucous membrane is performed using the cutting cautery to minimize bleeding. The skin is carefully approximated to the mucosal margin using fine silk. The results of this have been gratifying in our experience. One levatorplasty was performed with good results in improving bowel control.[10]

Conclusions

A clinical evaluation of 90 patients with anorectal malformations suggests that the current results leave considerable room for improvement in achieving the goal of bowel continence compatible with normal development and social activity. Careful identification of the abnormality is necessary to determine the proper choice of procedure, its timing and the follow-up management. Follow-up management of the postoperative patient is critical.

For anoperineal fistulas in males and females, the cutback anoplasty is a satisfactory procedure which can be done in the neonatal area. The choice of procedure for the female with an anovestibular or anovulvar fistula remains somewhat uncertain, but our tendency would be to support the perineal transplant anoplasty.

The problem of the large, poorly functioning rectosigmoid segment in the patient with anorectal malformations appears to need more study and clarification, particularly the differentiation of the hypertrophied bowel secondary to obstruction and the primarily defective bowel which is lax and flabby. In some patients, resection of this segment at the time of definitive repair or as a secondary procedure appears to be desirable.

The improvement of operative techniques of anocolonic anastomosis to avoid both postoperative stricture and excessive mucous membrane seems desirable. The importance of prolonged dilatation of the anoplasty to a relatively large aperture size appears important in attaining normal control.

Permanent colostomy may offer a desirable alternative to some patients with sacral neurological deficits or for patients with loss of muscle and nerve function from unsuccessful reconstructive surgery.

References

1. Arhan, P., Faverdin, G., Dubois, F., et al.: Manometric Assessment of Continence After Surgery for Imperforate Anus. J. Pediatr. Surg., 11:157, 1976.
2. Bill, A. H., Jr. and Johnson, R. J.: Failure of Migration of the Rectal Opening as the Cause for Most Cases of Imperforate Anus. Surg. Gynecol. Obstet., 106:643, 1958.
3. Boe, J., Knutrud, O. and Sommerschild, H. C.: Anal Atresia. Z. Kinderchir., 14:171, 1974.
4. Brandeskey, G. and Holschneider, A. M.: Operations for the Improvement of Faecal Incontinence. Prog. Pediatr. Surg., 9: 105, 1976.
5. Brent, L. and Stephens, F. D.: Primary Rectal Ectasia—A Quantitative Study of Smooth Muscle Cells in Normal and Hypertrophied Human Bowel. Prog. Pediatr. Surg., 9:41, 1976.
6. Browne, D.: Some Congenital Deformities of the Rectum, Anus, Vagina and Urethra. Ann. R. Coll. Surg. Engl., 8: 173, 1951.
7. deVries, P. A. and Friedland, G. S.: The Staged Sequential Development of the Anus and Rectum in Human Embryos and Fetuses. J. Pediatr. Surg., 9:755, 1974.
8. Gross, R. E.: The Surgery of Infancy and Childhood. Philadelphia, Saunders, 1953, pp 348–368.
9. Kiesewetter, W. B. and Chang, J. H. T.: Imperforate Anus: A Five to Thirty Year Follow-up Perspective. Prog. Pediatr. Surg., 10:111, 1970.
10. Kottmeier, P. K. and Dziadiw, R.: The Complete Release of the Levator Ani Sling in Fecal Incontinence. J. Pediatr. Surg., 2:111, 1967.
11. Limberg, A. A.: Design of Local Flaps. Mod. Trends Plast. Surg., 2:60, 1966.
12. Niloff, P. H., Gelfand, M. M. and Strean, G. J.: Imperforate Anus With Rectovaginal Fistula in an Adult. Can. J. Surg., 3:248, 1960.
13. Nixon, H. H. and Puri, P.: The Results of Treatment of Anorectal Anomalies: A Thirteen to Twenty-year Follow-up. J. Pediatr. Surg., 12:27, 1977.
14. Parkkulainen, K. W., Hjelt, L. and Sulamaa, M.: Anal Atresia Combined with Aganglionic Megacolon. Acta Chir. Scand., 118:252, 1959–1960.
15. Potts, W. J.: The Surgeon and the Child. Philadelphia, Saunders, 1959, pp 203–213.
16. Santulli, T. V., Kiesewetter, W. B. and Bill, A. H., Jr.: Anorectal Anomalies: A Suggested International Classification. J. Pediatr. Surg., 5:281, 1970.
17. Santulli, T. V., Schullinger, J. N. and Amoury, R. A.: Malformations of the Anus and Rectum. Surg. Clin. North Am. 45:1253, 1965.
18. Smith, E. D.: The Identification and Management of Anorectal Anomalies. The Factors Insuring Continence. Prog. Pediatr. Surg., 7:40, 1976.
19. Smith, E. I. and Gross, R. E.: Unpublished data.
20. Sommerschild, H., Knutrud, O. and Fretheim, B.: Anorectal Anomalies. Acta Chir Scand., 127:536, 1964.
21. Stephens, F. D. and Smith, E. D.: Ano-rectal Malformations in Children. Chicago: Yearbook Publishers, 1971, pp 23, 172–211, 258–273.
22. Swenson, O. and Grana, L.: Long-Term Results of Surgical Treatment of Imperforate Anus. Dis. Colon Rectum, 5:13, 1962.

DISCUSSION

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): (Slide) Since I agree with Dr. Smith in his approach, and his results are similar to ours, I thought it would be most useful if I emphasized some of the special aspects of the anatomy of the lower rectal canal, which may be abnormal in patients with imperforate anus. It is the child who is incontinent in whom studies are often helpful to us in the evaluation of eventual function.

(Slide) In the lower rectal canal are the three important elements of fecal continence: the puborectalis sling, the intrinsic sphincter, and the extrinsic sphincter. In the children with low pouch rectal atresia, both the levator sling and the intrinsic sphincter are present, and in almost all cases so is the extrinsic sphincter. So it is a matter of getting an opening in the right place. These children should have good results, as has been emphasized by Dr. Smith and his colleagues.

On the other hand, in the high-pouch children the pouch lies above the levator sling, and thus there is both an absence of the intrinsic sphincter and a lack of normal relationship to the puborectalis sling, although there usually will be an extrinsic sphincter muscle. Thus, the operative procedure is more complicated, and the results are predictably poorer.

In our evaluation of these patients, we have found the use of balloon manometrics very helpful. This is the set-up that has been used in our clinical research laboratories for a number of years. The balloon present at the area of the lower sigmoid, or rectal canal, instigates the stimulus for normal defecation, and at this point a balloon senses the intrinsic sphincter, and here the intrinsic sphincter.

Children are evaluated who have continuing problems with incontinence. This test may make it possible to pick up some of the abnormalities which are present. For example, in a patient with imperforate anus, type 1: the low pouch—who was continent and studied, normal relaxation of the internal sphincter occurs, just as it should. This is followed by contraction of the external sphincter, confirming the fact that this child should have a normally functioning lower rectal canal.

On the other hand, in a patient with an imperforate anus of the high pouch (type 3) there can be continence, even though, of course, there will not be an internal sphincter. The extrinsic sphincter may work appropriately, and with the proper positioning of the rectum in the levator sling, these children can be normally continent.

(Slide) Finally, a group of patients with imperforate anus of type 3 may be incontinent. Many of them have bizarre types of activity at the intrinsic sphincter area—of course, there is no real anatomic sphincter at this level, since this is a pulled-through bowel —but if they do not have normally functioning extrinsic sphincters, then there is no possibility that they can have true continence.

These children should be very carefully studied, to see whether they do indeed have an extrinsic sphincter which was not identified initially; they can benefit from repositioning of the anus.

If this is carried out, many of these children can become continent, and I think it is imperative that we study them carefully, because if they have the anatomic wherewithal, they can still be reconstructed. If not, as pointed out by Dr. Smith and his group, perhaps we should be considering more seriously the performance of a colostomy, which can be cared for very nicely on the abdomen, but not between the legs.

Dr. Judson G. Randolph (Washington, D. C.): I rise simply to emphasize two points which Dr. Smith has made so nicely in his paper.

No. 1, We still have a lot to learn about properly reconstructing these children. I'm sure you noticed that in his carefully followed patients nine, or an overwhelming number of the males with the high pouch, were classified as poor results.

Now, this, first of all, is honest; and secondly, comes from someone who has been interested in this problem a long time. Dr. Smith did one of the early fundamental studies on the anatomy and embryology of the rectum, and the anus, which is a classic.

All of you may not know that Dr. Jonathan Rhoads made a tremendous contribution with the abdominoperineal pull-through concept in 1947. And here we are, 30 years later, with poor surgical results in some patients.

An important point, I think, to be derived here is that the casual surgeon is not going to achieve the same results as someone who has given a lifetime to this study, such as Dr. Smith.

The second thing that should be emphasized is that a rectal function can sometimes be improved by reoperation. The objective is relocation of the rectum in the levator sling. In these high anomalies the levator sling snaps forward on the prostate, sort of like a slingshot. For some patients who have not achieved continence after early operations, we have been able through a sacroperineal approach to find this muscle and pull it back, and reposition the rectum within it, thereby achieving continence in some youngsters. This approach certainly should be attempted before consigning the child to a colostomy.

Dr. Richard C. Miller (Jackson, Mississippi): I rise to emphasize three points. Firstly, stenoses following repair of both high and low anomalies should be anticipated in a significant number of the patients, just as Dr. Smith has mentioned. These may be prevented in large measure by early dilatation of the new anus. We use Hegar dilators as soon as the anocutaneous suture line has healed, and send the dilators home with the mother, who dilates the baby once a day, as she changes his diapers, until the anus is soft and pliable. If the patient has a colostomy, colostomy closure is delayed until all tendency toward stricture has passed.

Secondly, the contributions of Mr. F. Douglas Stephens, particularly in regard to the importance of the puborectalis sling for continence, cannot be overemphasized. He devised the sacrococcygeal-perineal approach (slide) to the sling, and recommended that the bowel be brought down anterior to and inside the sling, as the other discussants have mentioned. This is the drawing from Mr. Stephens' textbook, which was published in 1963.

Using the Stephens procedure for all cases of high imperforate anus—that is, anorectal agenesis, with or without rectourethral or rectovaginal fistula—we have been able over the last 13 years to accomplish all pull-through procedures for the high anomaly via the sacrococcygeal-perineal route, without the necessity of an abdominal incision whatever. Only in those few cases, where the colon ends at a higher level and the fistula goes into the bladder, has the additional abdominal incision been necessary.

All of the patients with high anomalies have had a colostomy in the newborn period, and the infant, about a year of age, is admitted for the pull-through. (Slide) The anterior aspect of the patient is prepared, and a urethral metal sound is put in place. (Slide) The patient is turned over, and the posterior aspects are prepped and draped. (Slide) The sound is left exposed, so that it may be manipulated during the procedure, and the urethra easily identified.

The sacrococcygeal midline incision is made, and the coccyx is divided. The presacral space is entered. (Slide) The sling is dissected with a right angle clamp, and a perineal incision is made.

A Penrose drain is brought through the tunnel inside the sling. The sling may be seen as a very definite and real structure. (Slide) It is a real bundle of muscle, and the bowel must go down inside the sling. The blind ending portion of the rectum is then dissected, and any fistula is taken down.

Sutures are placed in the end of the bowel, and the blind end is pulled down through to the perineum, and one can see it appearing here at the perineal incision line. (Slide)

One can observe the bowel as it is pulled down to see it very definitely going down inside the sling. That is most important.

(Slide) Finally, the anus is sutured with interrupted sutures, and the sacral wound is closed with a simple drain, and anal dilatations are then begun as soon as healing has taken place down here, and the colostomy is closed only several months later, after the new anus is soft and pliable.

The third point that I would like to make is in regard to redundant mucosa. It has never been a problem with the Stephens' operation. There is simply not enough bowel to pull down to get excess mucosa. In fact, as healing proceeds, the anal skin is often drawn up into the anal canal, and a puckering of the anus often appears, sometimes producing an almost normal appearing anus.

Dr. E. Ide Smith (Closing discussion): There is no question in my mind, and those of my colleagues, that manometry will play an important role in the future evaluation of these children, and will help us to better design operations which best suit this abnormality.

Dr. Randolph asked me whether doing an initial "cutback" in a female with an anovestibular or anovular fistula, in whom one does a transplant later, troubles you in your second operation. I don't think that it does, in those that we have done this way. But as I mentioned, I'm not totally happy with the results that we have in this group.

I would certainly agree with three points that Dr. Miller made. First, I think dilation probably is a very much more important than we initially felt that it is. It's a very great problem in a population which is predominantly rural.

Secondly, the few patients that we had with sacral approaches are doing quite well. They are only a few, but anecdotally they seem to do well.

The same is true with the protection of the anastomosis by a colostomy. The few patients that we have in which a protective colostomy was done are doing well, and appear to have healed quite satisfactorily.

DALMANE®
(flurazepam HCl) Ⓒ IV

One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:
Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

> ***Usage in Pregnancy:*** **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, limit initial dosage to 15 mg to preclude oversedation, dizziness and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.

Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

REFERENCES: 1. Meyer JA, Kurland KZ: *Milit Med 138*:471-474, Aug 1973. 2. Feffer HL, Gibbons B: *Med Times 101*:130-135, Aug 1973. 3. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. 4. Warfarin Study: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. 5. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641. 6. Moore JD, Weissman L: *J Clin Pharmacol 16*:241-244, May-Jun 1976. 7. Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

ROCHE

ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

Efficacy.*

*proven relief when surgical patients require sleep medication[1,2]

Tonight.†

†significant efficacy the first night proved in paired-night studies[3]

Dalmane (flurazepam HCl) offers more safety benefits for your patients than barbiturates do. In contrast to barbiturates, Dalmane may be administered to patients on chronic warfarin therapy. Studies have shown no unacceptable fluctuation in prothrombin time.[4,5]

Dalmane is compatible with many common laboratory tests and does not interfere chemically with them.[6,7] (Alterations have been reported due to pharmacological effects; see Adverse Reactions section of product information.)

Please see preceding page for a summary of product information.

No other hypnotic has been evaluated as comprehensively as Dalmane. Sleep laboratory studies alone account for more than 1400 subject-nights.[3] These studies provide objective documentation of the hypnotic efficacy of Dalmane for short-, intermediate- and longer-term administration in adults of all ages…without repeated dosage during the night or increased dosage from night to night. The usual adult dosage of Dalmane is 30 mg *h.s.*, but 15 mg may suffice in some patients and is the initial recommended dosage in elderly or debilitated patients, to help preclude oversedation, dizziness or ataxia.

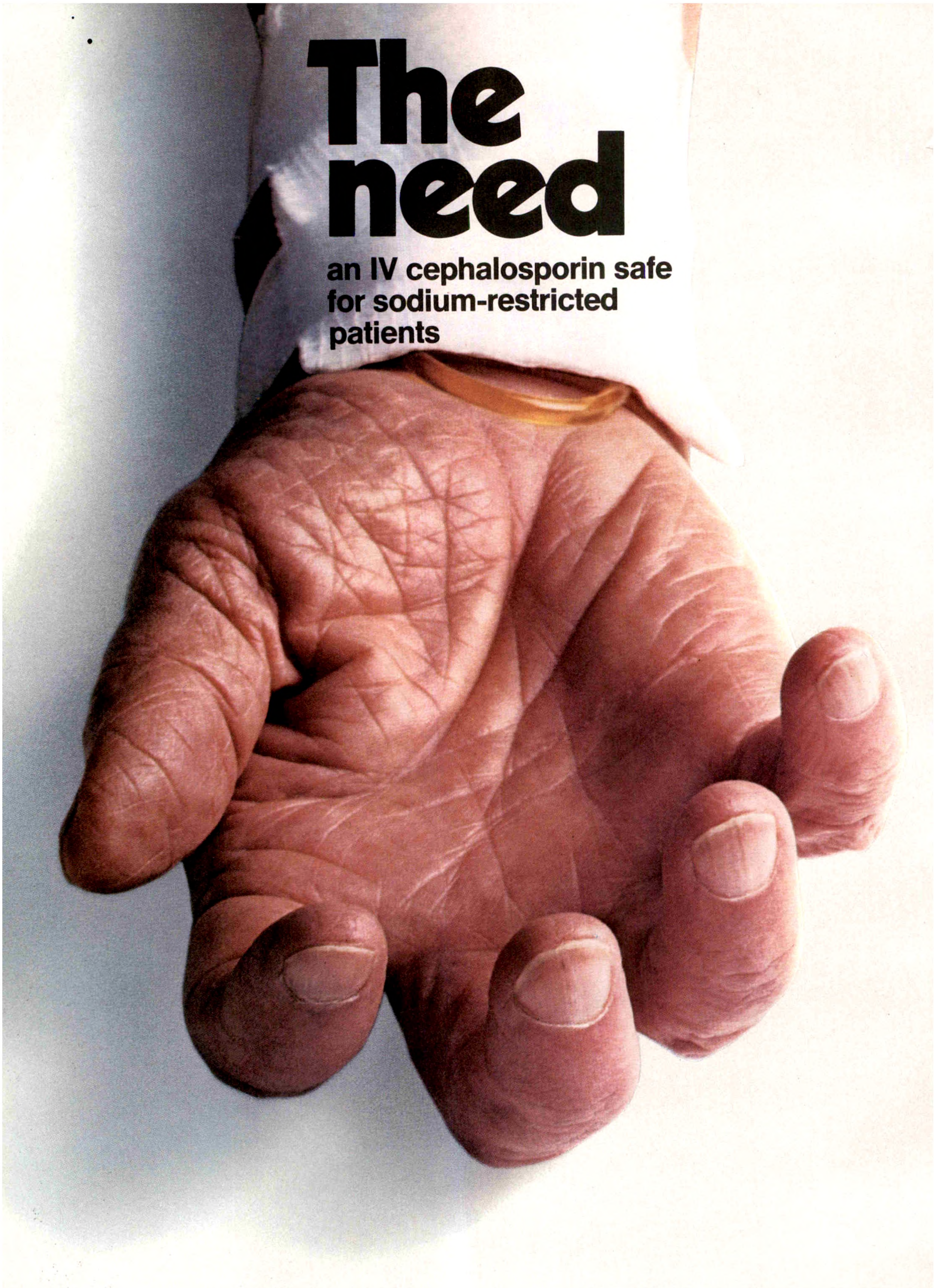
DALMANE®(flurazepam HCl)Ⓒ IV

also provides proof of no chemical interference with many common laboratory tests[6,7]

15-mg and 30-mg capsules

ROCHE

Computer-generated translation of color photography depicts the "awake" portion realistically, and the "asleep" portion in solarized form.



The need

an IV cephalosporin safe for sodium-restricted patients

The response

New Sodium-Free

velosef®
for infusion

STERILE CEPHRADINE

New formulation

- *Available as 2 g Cephradine* in 200 ml infusion bottles
- *Easy to prepare*—simply add 150 ml or 200 ml of diluent to constitute, for approximate concentrations of 13.3 mg/ml or 10 mg/ml of cephradine, respectively.
- *Same broad range of indications** as the other form of parenteral cephradine

New advantages

- *Enables you to treat serious susceptible infections* in patients whose sodium intake should be restricted*
- *Solutions stable* for up to 48 hours at room temperature or 1 week at 5° C.

New compatibility

- *Can be admixed with Lactated Ringer's Injection U.S.P.*, and most other commonly used intravenous fluids

*See Indications Section of Brief Summary on next page for a list of indications and susceptible organisms.

New Sodium-Free
velosef®
for infusion
STERILE CEPHRADINE

DESCRIPTION: Velosef for Infusion (Sterile Cephradine) is sterile cephradine, a powder for constitution available in infusion bottles containing 2 g cephradine.

INDICATIONS: This drug is indicated for the treatment of serious infections when due to susceptible strains of designated microorganisms as follows: Respiratory Tract Infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Klebsiella* sp., *H. influenzae, Staphylococcus aureus,* and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Urinary Tract Infections due to *E. coli, Pr. mirabilis,* and *Klebsiella* sp.; Skin and Soft Tissue Infections due to *S. aureus* and group A beta-hemolytic streptococci; Septicemia due to *Streptococcus pneumoniae, S. aureus, Pr. mirabilis,* and *E. coli.*

Note: Culture and susceptibility tests should be initiated prior to and during cephradine therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin C derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including fatal anaphylaxis after parenteral use).*

Use cautiously and only when absolutely necessary in persons who have demonstrated some form of allergy, particularly to drugs. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine; administer oxygen, I.V. steroids, and airway management (including intubation) as indicated.

Usage in Pregnancy and Lactation: Although no teratogenic or anti-fertility effects were seen in reproduction studies in mice and rats receiving up to four times the maximum human dose, the safety for use in human pregnancy has not been established; weigh benefits in pregnant women against possible risk to the fetus. Cephradine is secreted in breast milk during lactation.

Usage in Infants: Although this drug has been used effectively in infants, consider the benefits to risks ratio of the drug in the treatment of infants one month to one year of age since all laboratory parameters have not been extensively studied in this age group. Since safety for use in premature infants and in infants under one month of age has not been established, use of cephradine by infusion should be based on careful consideration of the benefits of the drug against the risk involved.

PRECAUTIONS: Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy.

Use lower daily dosage of sterile cephradine in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be conducted since cephradine in the usual recommended dosage will accumulate in the serum and tissues.

To detect any side effects or unusual manifestations of drug idiosyncrasy, follow patients carefully. Discontinue drug and treat with the usual agents (e.g., pressor amines, antihistamines or corticosteroids) if a hypersensitivity reaction occurs.

After treatment with cephradine, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®. As with other cephalosporins, positive direct Coombs tests have been reported infrequently.

Change injection site at appropriate intervals during long-term therapy to reduce risk of phlebitis from intravenous infusion.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I.—glossitis, nausea, vomiting, diarrhea or loose stools, tenesmus, abdominal pain. Skin and Hypersensitivity Reactions—mild urticaria or skin rash, edema, erythema, pruritus, joint pains, drug fever. Blood—mild, transient eosinophilia, leukopenia and neutropenia. Liver—elevated SGOT and SGPT have been observed in approximately 10% and 2% of patients respectively; elevated total bilirubin, alkaline phosphatase and LDH have been observed in a few cases; in most cases, values tended to return to normal after the end of therapy. Renal—mild rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old and in children under three. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others—headache, dizziness, dyspnea, paresthesia, candidal overgrowth, candidal vaginitis, hepatomegaly (isolated instances), and thrombophlebitis at injection site.

For full prescribing information, consult package insert.

HOW SUPPLIED: Available in intravenous infusion bottle (200 ml size) containing 2 g cephradine.

© 1978 E.R. Squibb & Sons, Inc. 788-501

SQUIBB® 'The Priceless Ingredient of every product is the honor and integrity of its maker.' ™

Selection of Treatment in the Management of Thyrotoxicosis in Childhood and Adolescence

ARDEN L. HOTHEM, M.D., COLIN G. THOMAS, JR., M.D., JUDSON J. VAN WYK, M.D.

From the Departments of Surgery and Pediatrics,
University of North Carolina School of Medicine and
North Carolina Memorial Hospital,
Chapel Hill, North Carolina

The management of 105 patients between the ages of three and 18 years, 83 females and 22 males, with thyrotoxicosis was reviewed retrospectively (1952–1976) with the intent of identifying criteria that would help predict response to therapy with antithyroid drugs and thereby permit earlier selection of alternative treatment. All patients were initially treated with antithyroid drugs. Twenty-six per cent (27) achieved remission with thioamides, 68% (72) underwent subtotal thyroidectomy with three patients requiring subsequent therapy with radioiodine, 6% (6) received radioiodine with one patient subsequently requiring subtotal thyroidectomy. Failure of remission after thioamide therapy was related to drug toxicity, persistent disease, noncompliance and recurrence after an initial remission. During the last decade there was earlier selection of subtotal thyroidectomy based on prior experience. The most significant discriminants were sex, age, and regression of thyromegaly. Ninety-one per cent of the males, 89% of children over 11 years of age and all patients who had no regression of their thyromegaly after a sustained period of control of their thyrotoxicosis by thioamide therapy received subtotal thyroidectomy or radioiodine therapy for control of their thyrotoxicosis. Recognition of these factors at the time of diagnosis should permit earlier selection of the most suitable treatment and expedite patient care. Subtotal thyroidectomy has a low morbidity and is effective treatment for thyrotoxicosis in adolescence and childhood.

THE TREATMENT OF THYROTOXICOSIS whether by medical management, surgery or radioiodine is reasonably effective. These modes of therapy are empirical with no direct attact upon the etiology of the disease. Selection of treatment is determined on the basis of age, sex, type of goiter, possibility of coexistent cancer, tolerance for drugs, uptake of radioiodine, family milieu and results of therapy. In most children and adolescents, antithyroid drugs have been the initial method of therapy.[2,5,8,13,16,26] Thirty to 60% of juvenile patients can be treated satisfactorily with antithyroid drugs. Failure of treatment is related to a) persistent disease despite drug control of the hypermetabolism, b) relapse after an initial remission, c) failure of the patient to follow the prescribed regimen, and d) drug toxicity. Partial ablation of thyroid function by subtotal thyroidectomy or radioactive iodine have also been used as definitive treatment. Usually these methods have been advised only after a remission has not been achieved with antithyroid drugs. Because of the limited experience of most observers and differences in the reported results of therapy, there is no unanimity regarding criteria for selection of definitive treatment at time of diagnosis.

This paper reviews our experience in the management of children and adolescents with thyrotoxicosis with the intent of identifying criteria for selecting at outset that form of therapy which would be most suitable for a particular patient. The establishment of prognostic criteria would permit antithyroid drugs to be administered to those patients who had a reasonable expectation of remission. Surgical or radioiodine therapy could then be given to the remainder of the patients with less delay in their recovery. Factors that were evaluated included age, sex, severity of disease, and change in thyroid gland with drug therapy.

This is a retrospective study of a 24 year experience. During this period there has been a change in attitude, thinking and evolution of our approach to the management of this disease. During the past decade subtotal thyroidectomy has been advised at a much earlier time in the disease, particularly in those patients who because of prior experience seemed highly unlikely to undergo remission on antithyroid drug treatment alone.

Patient Data

One hundred and five patients between the ages of three and 18 years (83 girls and 22 boys) treated by the pediatric and surgical attending and house staff at the

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Reprint requests: Colin G. Thomas, Jr., M. D., Department of Surgery, University of North Carolina School of Medicine, Chapel Hill, North Carolina, 27514.

0003-4932-78-0600-0593-0075 © J. B. Lippincott Company

TABLE 1. *Patient Data*

Race		
Black		55 (52%)
White		48 (46%)
Indian		2 (2%)
Total		105
Family History		
Thyrotoxicosis		25 (23%)
Goiter		29 (28%)
Thyroid cancer		2 (2%)
Total (105)		56 (53%)
Age		
	Mean	Range
Entire group (105)	12.0	3–18 Yrs.
Girls (83)	11.8	3.5–18 Yrs.
Boys (22)	12.6	3–17 Yrs.

North Carolina Memorial Hospital from 1952 through 1976 provide the clinical material. Race, family history and age data can be found in Table 1. Numbers of patients treated with antithyroid drugs, surgery, and radioiodine are indicated in Table 2. Tables 3 and 4 enumerate the differing forms of therapy by sex and indications for alternative treatments. All children had some degree of thyromegaly. This was graded on a scale of 1–4, 1—no enlargement, 2—twice the normal size, 3—triple the normal size, *etc.* (Tables 5 and 6).

All patients were initially treated with antithyroid medications. Twenty-six per cent (27) underwent remission with antithyroid drugs, 68% (72) were operated upon with three patients requiring subsequent therapy with radioactive iodine. Six per cent (6) received radioiodine with one patient subsequently requiring partial thyroidectomy. Antithyroid drug were discontinued and alternative treatments were selected in four patients because of drug reactions (rash or granulocytopenia), and in 29 patients because of their failure to comply with the prescribed treatment regimen (22 females and seven males). Forty-two patients (32 females, 10 males) were judged to have continuing disease after one or more years of antithyroid medications. Included in this group were four patients who became pregnant. Subtotal thyroidectomy was performed primarily because of difficulty in controlling the hypermetabolic state due to noncompliance or because of unwillingness on the part of either the physician or patients to continue medical therapy. The most important factor influencing the pediatric endocrinologist who recommended surgery was a significantly enlarged gland that failed to decrease in size with medical therapy. Time for remission of the disease with thioamide treatment ranged from one to 84 months with a mean of 24.6 months. Therapy with radioiodine was carried out in those patients who required an alternative form of therapy but who refused subtotal thyroidectomy or were considered poor surgical risks. Three patients with recurrence after subtotal thyroidectomy were also treated with radioiodine.

TABLE 2. *Definitive Treatment*

	Total Patients	%
Remission on antithyroid drugs	27	26
Subtotal thyroidectomy	72	68
Additional treatment with ^{131}Iodine	3	
Radioiodine treatment	6	6
Additional thyroidectomy	1	

TABLE 3. *Treatment of 83 Females*

	Total Patients	%
Remission with antithyroid drugs	25	30
Subtotal thyroidectomy	55	66
Allergic drug reaction	1	
Continuing disease	32	
Noncompliance	22	
Additional Rx with ^{131}I	3	
Radioiodine therapy	3	4
Noncompliance	2	
Drug reaction	1	

Age, sex, severity of disease and change in gland size on antithyroid medication were evaluated in an attempt to identify criteria which might have prognostic value in the selection of treatment.

Age

The age at the time of diagnosis of thyrotoxicosis (clinical and biochemical criteria) ranged from three to 18 years with a mean of 12. The girls had an average age of 11.8 years ranging from 3.5 to 18. The boys averaged 12.6 years, ranging from 3 to 17 (Table 1). Girls undergoing remission had a mean age of 9.1 years as contrasted to those with persistent disease with a mean age of 12 (Table 5). The two males who under-

TABLE 4. *Treatment of 22 Males*

	Total Patients	%
Remission with antithyroid drugs	2	9
Subtotal thyroidectomy	17	77
Continuing disease	10	
Noncompliance	7	
Radioiodine (I^{131})	3	14
Allergic drug reaction	2	
Noncompliance	1	

TABLE 5. *Thyroid Gland Response to Antithyroid Medication (83 Females)*

	Mean Age	Initial Size	Final Size	Change
Persistent disease (32)	12	3.8×	3.9×	↑0.1
Noncompliance (24)	9.1	3.7×	3.7×	0
Remission (25)	9.1	3.5×	1.6×	↓1.9
Granulocytopenia (2)	10.5	3.5×	2.0×	↓1.5

The normal thyroid gland in adults is estimated to weigh 20 grams and is impalpable. Size of the gland was estimated by hyperextending the neck, outlining the palpable gland in ink, and converting this tracing to the patient's record. The limitations of this technique are obvious because of the methodology and the variation between observers.

went remission were also three years younger than their cohorts (Table 6). Fifty per cent of 40 patients (35 female, five male) under 11 years of age underwent remission on antithyroid drugs. Fifty-six per cent of the 35 females and 20% of the five males in this age group were successfully managed by this means. In contrast, only 11% of 65 patients over 11 years achieved remission on antithyroid drugs with 13% of 48 females and 6% of 17 males responding (Table 7).

Sex

Thirty per cent (25/83) of the females and 9% (2/22) of the males responded to medical therapy with remission. The remaining 58 females and 20 males required alternative treatment. Tables 3 and 4 indicate the methods of therapy and the reasons for surgical or radioiodine treatment.

Severity of Disease

There were insufficient data to determine whether severity of disease was a factor in determining response to antithyroid drug therapy.

Change in Gland Size

Girls in the noncompliant and persistent disease groups had essentially no change in gland size. Those undergoing remission realized nearly a two-fold decrease in thyroid gland size (Table 5). In 12 of these patients the thyroid regressed to normal size and in the remainder it was estimated at no greater than twice normal size. No patient underwent remission without regression of their goiter unless at the outset it was no more than twice normal size. In two of the patients developing granulocytopenia the gland decreased from 3.5 to two times normal in size (Table 5).

In the two male patients (9%), who were successfully treated medically (Table 6), there was a decrease in gland size. Most of the boys (82%) were in the persistent disease or noncompliant groups demonstrating essentially no significant size change in the thyroid gland (Table 6). In the two patients (9%) who developed a rash necessitating discontinuance of the antithyroid drugs, the gland decreased only from 3.5 to 3.0 times normal size.

TABLE 6. *Thyroid Gland Response to Antithyroid Medication (22 Males)*

	Mean Age	Initial Size	Final Size	Change
Persistent disease (10)	13.8	4.1×	4.5×	↑0.4
Noncompliance (8)	13.5	4.1×	3.5×	↓0.5
Remission (2)	10.1	3.5×	1.5×	↓2.0
Rash (2)	13	3.5×	3.0×	↓0.5

The overall results of therapy including complications are depicted in Table 8. Follow-up of these patients ranged from a few weeks to 14 years with a mean period of three years and a median of two years. Therefore, the low observed incidence of hypothyroidism represents a minimum figure. The incidence of postoperative hypothyroidism in this series is relatively low, *viz*, 12.5% (9/72). This is probably at a cost of a higher incidence of recurrent hyperthyroidism, *viz*, 4% (3/72). Because of the autoimmune nature of the disease, the incidence of hypothyroidism following ablative therapy whether radioactive iodine or subtotal thyroidectomy increases with the period of observation.

Discussion

The symptoms and findings associated with thyrotoxicosis during childhood and adolescence have been well described by others.[2,5,15,22,25] The clinical diagnosis can readily be confirmed with appropriate thyroid function tests. The major objective in treating thyrotoxicosis is to achieve a permanent euthyroid state as safely and as rapidly as possible. This can be done by one or a combination of methods: antithyroid medica-

TABLE 7. *Remission on Antithyroid Drugs Effect of Age and Sex*

Number Patients	Age/Yrs.	Percent Remission
40	<11	50.0
25 Female		56.0
5 Male		20.0
65	≥11	11.0
48 Female		13.0
17 Male		6.0

Cochran-Mantel-Halnszel test for significance indicates that age adjusted for sex is highly significant with females <11 years have a higher percentage of remission than males in either age group and females ≥11, Q = 16.23, $\alpha = .01$.

Sex adjusted for age is not significant for either age with present study and sample size. It may become significant for individuals <11 years in larger sample sizes.

TABLE 8. *Results of Treatment (105 Patients)*

	Euthyroidism	Hypothyroidism	Recurrent Hyperthyroidism	Hypopara-thyroidism	Cord Paralysis (Temporary)	Cord Paralysis (Permanent)
Antithyroid drugs (27)	26	1	—	—	—	—
Subtotal thyroidectomy (72)	63	9	3	2	5	2
Radioactive iodine (6)	3	3	1	—	—	—

tion, ablation by surgical excision or radioactive iodine. Optimum therapy for children with thyrotoxicosis remains undetermined. This is related to failure to identify the etiology of the disease and that all modes of therapy are associated with some risk and variable results.

Antithyroid drug treatment of Graves' disease is based upon the thesis that thyrotoxicosis is a self-limiting disease and with time will undergo spontaneous remission.[9] The duration from onset to remission ranges from months to years. This natural history is related to the observation that human thyroid stimulating immunoglobulins (HTSI) have been detected in virtually all cases of untreated Graves' disease and almost certainly are responsible for the hyperthyroidism of that disorder.[10] HTSI appears to be an autoantibody to thyroid constituents, a finding suggesting the prime change in Graves' disease to be an immune one. Pertinent is the change in HTSI from virtually 100% in the untreated patient to less than 50% in those treated with antithyroid drugs or radioiodine. Subtotal thyroidectomy has a dramatic effect on HTSI levels, reducing them to 15%.[10]

The nature of the disease requires lifelong surveillance regardless of the method of treatment. Late recurrence may develop (primarily following thioamide drugs) or hypothyroidism occur with any type of ablative therapy.

Currently, most pediatric endocrinologists advise control of the thyrotoxicosis with antithyroid drugs for a period of two to four years anticipating that 30–60% of patients will undergo remission.[5,8,26] There are no uniform criteria that permit prediction of patients most likely to undergo remission after completion of therapy. Small size of the thyroid at outset, regression of the size of the goiter during treatment, and restoration of a normal hypothalamic, pituitary, thyroid feedback mechanism have been cited as factors favoring remission.[1,5,9,13,19,22,23,25] Barnes and Blizzard have recently reported their results in 104 patients.[5] They use a 12 hour perchlorate discharge test to determine the least frequent dose schedule of antithyroid drugs required for disease control.[6] Sixty-eight per cent could be controlled on a single daily dose. They have used a one hour ^{131}Iodine uptake while the patient is on thioamide plus thyroid hormone as a guide to remission. Patients undergoing remission has been treated for a period greater than 24 months, had a one hour radioiodine uptake of less than 4% and decrease in gland size to normal or near normal. Patients with a one hour uptake of greater than 10% became hyperthyroid within four months after discontinuing antithyroid medication. In contrast to findings of Irvine and Stewart[17], elevated antithyroglobulin titers did not correlate with suppressibility or decrease in gland size. Their overall success rate on antithyroid medication was 61%. In patients undergoing subtotal thyroidectomy, hypothyroidism developed in 78% of those with elevated titers to antithyroid globulin antibodies and in 40% of those without elevated titers. The incidence of hypothyroidism in the 36 patients undergoing thyroidectomy was 65%.

The remission rate in adults treated with thioamides has been recently observed to be significantly decreased (50–20%)[27] over results in earlier studies.[9,13-14,16,23] This lower incidence of remission in the last two successive decades has also been observed in children by Barnes and Blizzard with a reduction from 77–53%.[5]

Partial thyroidectomy or radioactive iodine is advised in patients failing to undergo remission with antithyroid drugs, developing toxic reactions, or who cannot or will not follow a prolonged course of drug therapy. Usually surgical treatment has been reserved as a secondary approach. The major exception to this position has been Hayles who, based on the Mayo Clinic experience, advises subtotal thyroidectomy as primary therapy.[12] Experience with more than 200 children treated since 1934 indicates no mortality and no damage of recurrent nerves. One patient developed hypoparathyroidism. In 1950 they observed a recurrence rate of 10% and a 38% incidence of hypothyroidism. Since that time a more extensive resection has been carried out with a postoperative incidence of hypothyroidism of greater than 50% and two mild recurrences. Arnold, et al.,[4] and Kogut, et al.,[18] also advised subtotal thyroidectomy as primary therapy.

The reported incidence of complications and results of surgical treatment vary considerably, *i.e.*, a recurrence rate of 0–33% and hypothyroidism from 0–60%.[5] Mean figures from the literature indicate no operative mortality, an incidence of hypothyroidism of 35%, permanent hypoparathyroidism of 10% and recurrence of 6–10%.[11,19,22] Recurrences have been reported more than ten years postoperatively.[3,10] Altman reported total thyroidectomy in eight patients as a means of preventing recurrent disease with a complication rate no higher than with subtotal thyroidectomy.[3]

Radioactive iodine has been reported as primary treatment in relatively few children compared with adults.[5,20,21,24] The most common concerns related to radioactive iodine are the high incidence of hypothyroidism, the unknown hazard of genetic damage,[7] and the incidence of subsequent nodules. In a review of the literature (1975) the total number of patients reported was 273 with a follow-up period of one to 24 years.[20] Hyperthyroidism was controlled in 98% of the patients with a 51% incidence of hypothyroidism, a relapse rate of 2% with 2% developing nodules and 3% Hashimoto's thyroiditis. The incidence of nodules and thyroiditis was not uniform. Cancer occurred in two patients. No cases of leukemia have been reported. In the largest series (108 patients)[20,21] followed five to 24 years, the fertility rate and number of spontaneous abortions were no different than those of the general population. The frequency of congenital abnormalities in children of ^{131}Iodine-treated parents was not increased. Chromosome studies performed in 46 of 90 children born to parents previously treated with ^{131}Iodine detected no abnormalities.

In this series, antithyroid drugs (Propylthiouracil and Methimazole) were used at the outset, anticipating that remission would ensue in some patients. Twenty-six per cent of this series of patients (27/105) responded with a permanent remission (four of these required a second course) while one of these 27 patients ultimately became hypothyroid.

The groups that were most likely to undergo alternative therapy were: 1) boys (average age 13.6 years), with 91% (20 of 22) receiving other treatment; 2) patients over 11 years of age with 89% being treated by thyroidectomy or radioiodine; and 3) those who did not demonstrate a reduction in thyromegaly after control of their thyrotoxicosis by thioamides. Children who had persistence of thyromegaly of greater than two times normal after a sustained period of control of their thyrotoxicosis by medical treatment all required an alternative form of therapy.

Suppression of thyroid function has been used as a guide to the duration of treatment with antithyroid drugs as well as to predict which patients are most likely to have a sustained remission.[1,5] These tests presume a fall in thyroid stimulating immunoglobulins and restoration of a normal hypothalamic-pituitary-thyroid feedback mechanism. It would be difficult to conceive of this occurring without regression of thyromegaly. Consequently, regression in goiter size appears to be as reliable a criterion for duration of therapy and the likelihood of remission as these more sophisticated tests of thyroid autonomy.

The overall remission with thioamides in this series was 26%, representing primarily a high incidence of persistent disease, noncompliance and a changing attitude toward thyroidectomy. Thyroidectomy was advised at a much earlier time in the course of the disease during the past decade. Small goiter, regression in gland size and restoration of TSH-TH feedback mechanisms have all been cited as factors predicting a favorable outcome to antithyroid drugs. Our observations were striking in that these conditions prevailed predominantly in patients who were female and below 11 years of age. Chance of procuring remission in males and in females greater than 11 years was less than 15%. This has not been emphasized by previous observers.

The ideal method of treating children and adolescents with thyrotoxicosis has not been established. All current modalities are associated with significant side effects and/or complications. Overall management will be expedited by early selection of alternative methods of therapy in patients who are treated definitively with antithyroid drugs, failure of regression of thyromegaly constitutes an indication for other treatment. Subtotal thyroidectomy has low morbidity and is an effective method of treating hyperthyroidism in children and adolescents. Radioiodine is the least desirable form of therapy because of the unknown genetic hazards and the high incidence of hypothyroidism. Particularly is this pertinent in the noncompliant patient in whom the morbidity of hypothyroidism is significant.

References

1. Alexander, W. D., Harden, R. McG. and Shimmins, J.: Thyroidal Suppression by Triiodothyronine as a Guide to Duration of Treatment of Thyrotoxicosis with Antithyroid Drugs. Lancet, II:1041, 1966.
2. Allen, R. F., Rose, E. and Rose, E. K.: Juvenile Thyrotoxicosis. Pediatrics, 14:38, 1954.
3. Altman, R. P.: Total Thyroidectomy for Treatment of Graves' Disease in Children. J. Pediatr. Surg., 8:295, 1973.
4. Arnold, M. B., Talbot, N. B. and Cope, O.: Concerning the Choice of Therapy for Childhood Hyperthyroidism. Pediatrics, 21:47, 1958.
5. Barnes, H. V. and Blizzard, R. M.: Antithyroid Drug Therapy for Toxic Diffuse Goiter (Graves' Disease): Thirty Years Experience in Children and Adolescents. J. Pediatrics, 91:313, 1977.
6. Barnes, H. V. and Bledsoe, T.: A Simple Test for Selecting the Thioamide Schedule in Thyrotoxicosis, J. Clin. Endocrinol. Metab., 35:250, 1972.
7. Bross, I. D. and Natarajan, N.: Genetic Damage from Diagnostic Radiation, JAMA, 237:2399, 1977.
8. Green, W., Wessler, S. and Avioli, L. V.: Management of Juvenile Hyperthyroidism. JAMA, 213:1652, 1970.
9. Greer, M., Kammer, H. and Bouma, D. J.: Short-Term Antithyroid Drug Therapy for the Thyrotoxicosis of Graves's Disease. N. Engl. J. Med., 297:173, 1977.

10. Haibach, H. and Avioli, L. V.: Hyperthyroidism in Graves' Disease. Current Trends in Management and Diagnosis. Arch. Intern. Med., 136:725, 1976.
11. Hargraves, A. W. and Nicholson, W. F.: Adolescent Thyrotoxicosis. Br. J. Surg., 55:887, 1968.
12. Hayles, A. B.: Problems of Childhood Graves' Disease. Mayo Clin. Proc., 47:850, 1972.
13. Hershman, J. M.: The Treatment of Hyperthyroidism. Ann. Intern. Med., 64:1306, 1966.
14. Hershman, J. M., Givens, J. R., Cassidy, E. C. and Astwood, E. B.: Long Term Outcome of Hyperthyroidism Treated with Antithyroid Drugs. J. Clin. Endocrinol., 26:803, 1966.
15. Hung, W., Wilkins, L. and Blizzard, R.: Medical Therapy of Thyrotoxicosis in Children. Pediatrics, 30:17, 1962.
16. Ingbar, S. H. and Woeber, K. A.: *In* Williams, R. H. (ed.), Textbook of Endocrinology, 5th edition, Philadelphia, Saunders, 1974, pp. 163–184.
17. Irvine, W. J. and Stewart, A. G.: Prognostic significance of thyroid antibodies in the management of thyrotoxicosis. *In* Irvine, W. J. (ed.), Thyrotoxicosis, Baltimore, Williams and Wilkins, 1967, pp. 111.
18. Kogut, M. D., Kaplan, S. A., Collipp, P. J., et al.: Treatment of Hyperthyroidism in Children. N. Engl. J. Med., 272:217, 1965.
19. Reeves, T. S., Hales, I. B., White, B., et al.: Thyroidectomy in Management of Thyrotoxiocosis in the Adolescent. Recent Adv. Surg. 65:694, 1969.
20. Safa, A. M., Schumacker, O. P. and Antunez, A. R.: Longterm Followup Results in Children and Adolescents Treatment with Radioactive Iodine for Hypothyroidism. N. Engl. J. Med., 292:167, 1974.
21. Safa, A. M. and Schumacker, O. P.: Follow-up of Children Treated with ^{131}I. N. Engl. J. Med., 294:54, 1976.
22. Saxena, K. M., Crawford, J. D. and Talbot, N. B.: Childhood Thyrotoxicosis: A Long-term Perspective. Br. Med. J., 2: 1153, 1964.
23. Solomon, D. H., Beck, J. C., Vanderlaan, W. P. and Astwood, E. B.: Prognosis of Hyperthyroidism Treated by Antithyroid Drugs. JAMA, 152:201, 1953.
24. Starr, P., Joffee, H. L. and Oettinger, L.: Later Results of I^{131} Treatment of Hyperthyroidism in 73 Children and Adolescents: 1967 Follow-up. J. Nucl. Med., 10:586, 1969.
25. Van Wyk, J. J.: Nontoxic Goiters and Thyrotoxicosis in Childhood and Adolescence. Med. Times, 94:1317, 1966.
26. Vaidya, V. A., Bongiovanni, A. M., Parks, J. S., et al.: Twenty-two Years' Experience in the Medical Management of Juvenile Thyrotoxicosis, Pediatrics, 54:565, 1974.
27. Wartofski, L.: Low Remission after Therapy for Graves' Disease. Possible Relation of Dietary Iodine with Antithyroid Therapy Results. JAMA, 226:1083, 1973.

DISCUSSION

DR. SAMUEL ALONZO WELLS, JR. (Durham, North Carolina): Dr. Thomas and his associates have certainly acquired a very impressive series of patients. I would like to ask Dr. Thomas two questions.

Have you ever found it necessary to use only propranolol in preparing patients for surgery? We have had two patients who were allergic to both methimazole and propylthiouracil. Both were poorly controlled metabolically until propranolol was given. They were euthyroid during the preoperative period and had no difficulty during or after the operative procedure.

Do you really consider it a complication if these children turn out to be hypothyroid in the postoperative period? L-thyroxine replacement is so effective generally that I wonder if you do not risk having some of these children become hyperthyroid subsequently when trying to leave enough tissue to make them euthyroid postoperatively.

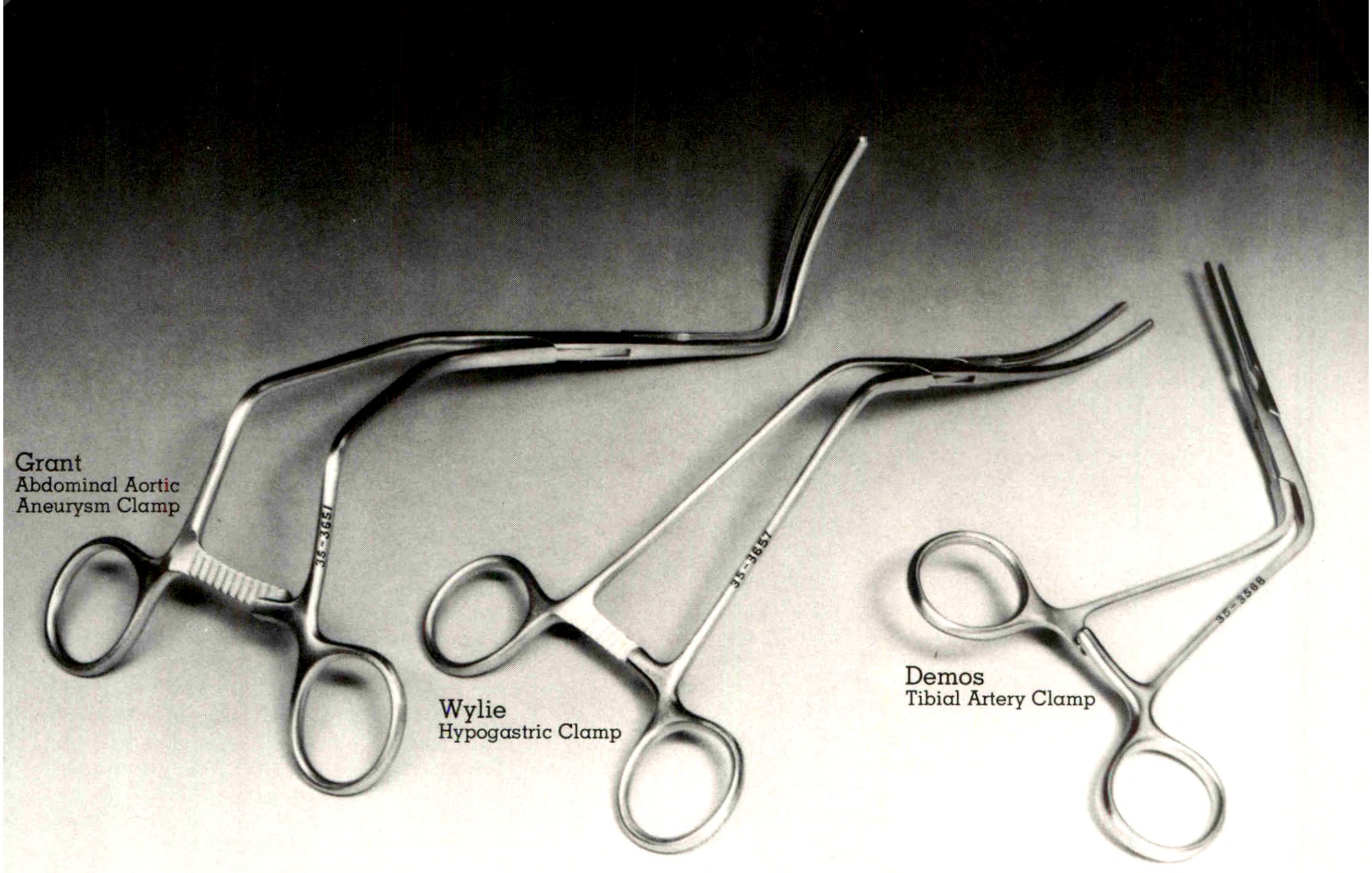
DR. COLIN G. THOMAS (Closing discussion): I want to thank Dr. Wells for his comments. He may be the only one that really understands the significance of this paper.

Yes, we have used propranolol in two ways. One is in the preoperative preparation of the patient who comes in for operation but who isn't quite euthyroid; and secondly, in the occasional patient who does not tolerate antithyroid drugs, using propranolol alone, or in association with Lugol's solution. This method has been quite effective.

Insofar as hypothyroidism being a complication, I do regard it as such. One of the advantages of subtotal thyroidectomy is, presumably, to have a lower incidence of hypothyroidism, as compared with a patient who receives radioactive iodine. Further, a number of our patients are noncompliant, and if they don't take thyroid medication after they are hypothyroid, then we have a very serious problem. This is one of the reasons for selecting thyroidectomy in lieu of radioactive iodine. I think we try to achieve euthyroid state, recognizing it may be difficult.

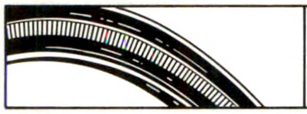
One of the things that may be helpful is to examine the thyroid gland histologically at the time of operation and identify the extent of thyroiditis that is present. We usually biopsy one lobe after it has been mobilized. If there is a high component of lymphocytes, then we may leave more thyroid gland on the opposite side than if that condition did not exist.

90% of all vascular clamps are developed at Pilling.



Pilling has been the craftsman behind almost every improvement in vascular clamps.

Pilling has more clamps than any other company. Only three of our recent clamps are shown above; yet our list is extensive and new designs are constantly in production. For aortic and peripheral vascular occlusion, *350 different Pilling clamps* match the anatomical considerations for almost every surgical approach you use.



Atraugrip® Serration. Complete vessel occlusion. With intimal protection.

Life-Lok® Construction. No riveted pin. Box lock won't break.

Every Pilling clamp gives you these exclusive benefits:

- Non-traumatic Atraugrip® jaw serrations — patented by Pilling and now widely imitated, grasp vessels firmly without crushing. Five different jaw patterns are available: Atraugrip®, Small Atraugrip®, Atraugrip® (2 x 3), Cooley, and Pediatric, 1mm. You get complete vessel occlusion *with intimal protection*.
- You've had box locks break. It'll never happen again. Pilling box locks are virtually indestructible — they will not break! Our Life-Lok® box lock construction protects your patient and assures confidence in your clamps.

We want to send you full specifications on the clamps that can enhance your surgical technique. Call us direct. We'll send you our 240 page catalog showing how Pilling clamps can do more for you in the operating room than any other clamps.

Call toll free. Ask for Pilling's latest catalog of vascular, thoracic, and cardiac instruments.

800-523-6507

215-643-2600 in Pennsylvania or write Mr. William Taylor at the address below.

◇ NARCO **PILLING**
A Division of Narco Scientific
Delaware Drive
Fort Washington, PA 19034 • U.S.A.

New books for the busy surgeon

. . . update your library today!

CORONARY ARTERY SURGERY

Authoritative and complete in its treatment of the subject, this book encompasses many aspects of coronary artery disease. Its main objective is to provide the surgeon with an authoritative guide to management from the highly experienced point of view of the authors. The surgeon will find precise, clinical information presented in a very logical and orderly fashion that greatly enhances the practical usefulness of the book. An abundance of information concerning use of the saphenous vein and the internal mammary artery as grafts, cannulation and extracorporeal circulation, choice of operative technique and site of distal anastomosis, exposure of the heart, methods of vascular anastomoses, and management of complications is presented. Many original drawings clearly illustrate these technical maneuvers. Other chapters deal with the various pathologic processes for which coronary artery bypass is useful, and the subtleties of coronary anatomy. Coronary angiography is treated according to the needs of the surgeon, correlating the angiographic and surgical findings. Among the chapters that discuss the scientific/clinical elements of coronary artery surgery, is a highly important chapter that deals with the humanistic aspects. Psychological considerations and the role of the psychiatrist and cardiovascular nurse specialist are highlighted. A method of informed consent—used over three years by the authors with excellent response from the patients—is also presented.

By **JOHN L. OCHSNER, M.D.**, and **NOEL L. MILLS, M.D.**, both of the Ochsner Clinic, New Orleans, Louisiana. *275 pp. (7 x 10), illus., 1978, $25.00.*

PROGRESS IN CARDIOLOGY. 6

This sixth volume of a popular series is a departure from the first five which were concerned with disparate subjects in cardiology. It is devoted exclusively to coronary revascularization. Many European and American cardiologists and cardiac surgeons examine all the major aspects of the subject from surgical techniques in coronary artery bypass grafts to sophisticated hemodynamic and angiographic evaluation of the left ventricular function before and after coronary revascularization.

Edited by **PAUL N. YU, M.D.**, University of Rochester School of Medicine and Dentistry, Rochester, New York; and **JOHN F. GOODWIN, M.D.**, Royal Postgraduate Medical School, London, England. (31 Contributors). *211 pp. (7 x 10), illus., 1977, $15.00.*

THE HAND: Surgical and Non-surgical Management

A distinguished group of contributors, each especially well qualified to write in his assigned area, have joined the authors in presenting a definitive, up-to-date text on diagnosis and treatment of hand disorders. This wealth of expertise, together with an abundance of specially prepared illustrative material, combine to form a highly clinical, practical study of the "state of the art." Thirty chapters provide thorough coverage of stiffness, pain, common dermatological disorders, pitfalls, psychological aspects of hand disorders, anesthesia, and biology of repair. Trauma, degenerative diseases, congenital anomalies and tumors, disorders of the musculotendinous, skeletal and neurological systems are dealt with in detail. Also included are chapters covering facilities for treatment, examination and diagnostic procedures, pre- and postoperative care, incisions and wounds, dressings and splints, wound healing, and disability evaluation.

Edited and with contributions by **EUGENE S. KILGORE, JR., M.D.**, University of California Medical School, San Francisco, California; and **WILLIAM P. GRAHAM, III, M.D.**, Pennsylvania State University College of Medicine, Hershey. (19 Contributors). *502 pp. (8-1/2 x 11), illus., 1977, $48.50.*

DEVELOPMENTS IN DIGESTIVE DISEASES: Clinical Relevance. 1

Eleven chapters which constitute this book present the reader with new and meaningful developments in the field of digestive diseases with the emphasis on their relevance to the practice of medicine. The contributors bring recognized expertise and authority to their reviews.

Edited and with contributions by **J. EDWARD BERK, M.D., D.Sc.**, University of California, Irvine, California. (21 Contributors). *199 pp. (7 x 10), illus., 1977, $22.50.*

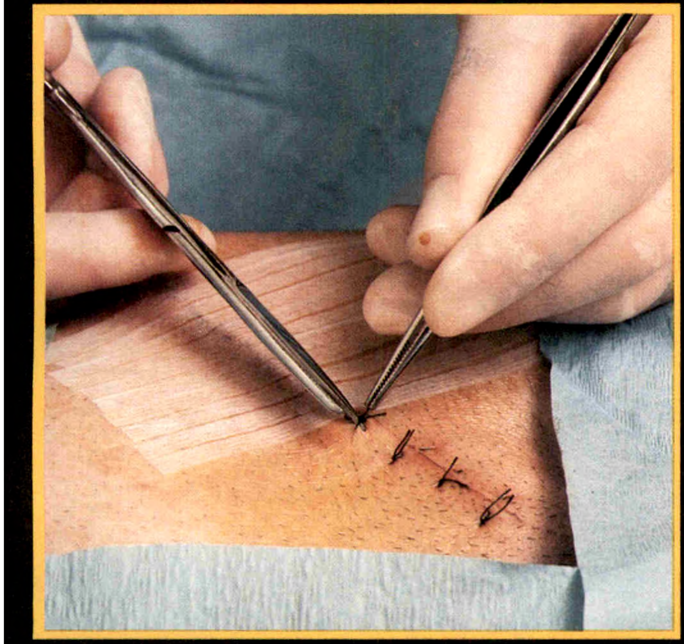
Order from your favorite bookstore or:

LEA & FEBIGER

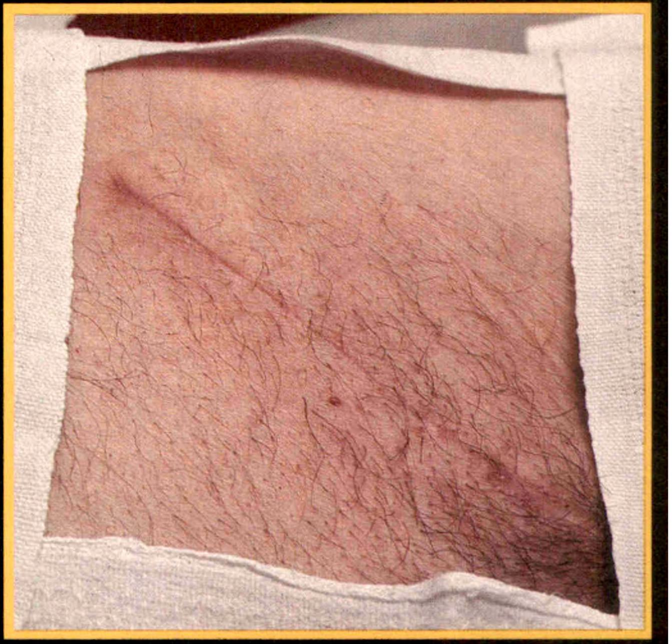
WASHINGTON SQUARE / PHILADELPHIA, PA. / 19106

72-HOUR SUTURE REMOVAL

Replace sutures with STERI-STRIP® Skin Closures for enhanced wound healing, a finer scar, less chance of infection.[1]



Sutures removed 72 hours postoperatively.



38 days postop.

STERI-STRIP Brand Skin Closures make suture removal possible at a point that is most beneficial to the wound – 72 hours postoperatively.[2,3] The wound develops tensile strength faster due to the uniform stress applied to collagen fibers and fibrils, causing rapid fiber orientation.[4] When sutures are removed early STERI-STRIP Skin Closures provide firm support, reduced suture effects and greater patient comfort.

Contact your 3M Surgical Products representative for further information. 3M Surgical Products Division, 3M Center, St. Paul, MN 55101.

Free Wound Support Kit

Your personal Wound Support Kit is now available. Simply return the attached card or contact your 3M Surgical Products representative.

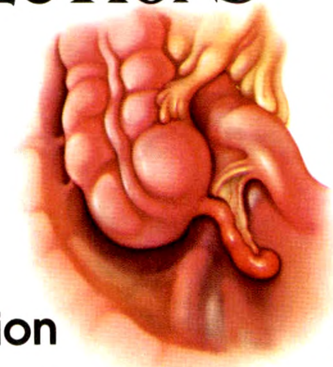
Offer Limit: 1 Free Wound Support Kit
Good until Dec. 31, 1978.

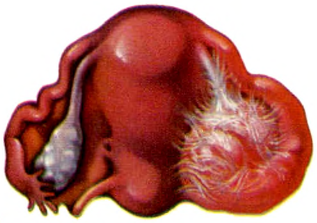
REFERENCES:

1. Edlich RF, Rodeheaver G, Kuphal J, deHoll JD, *et al*: Technique of closure: Contaminated wounds. *J Am Coll Emer Phys* 3:375-381, 1974.
2. Brunius U, Akren Chr: Healing impairment of skin incisions closed with silk sutures. *Acta Chir Scand* 135:369-381, 1969.
3. Lewis JR, Jr: Facial scars resulting from vehicular accidents. *Clinics in Plastic Surgery* 2:143-166, 1975.
4. Forrester JC, Zederfeldt BH, Hayes TL, Hunt TK: Wolff's Law in relation to the healing wound. *J Trauma* 10:770-779, 1970.

Upjohn

THE BIPHASIC NATURE OF SERIOUS INTRA-ABDOMINAL/PELVIC INFECTIONS





Introduction

The biphasic clinical nature of serious intra-abdominal and female pelvic infections may be related to sequential dominance first of aerobes and then of anaerobes. Antimicrobial coverage of both aerobes and anaerobes should be considered during all stages of serious intra-abdominal and female pelvic infections.

The majority of these infections are polymicrobial. During the early, toxic phase, aerobes are

Acute Phase:
Peritoneal Response

Peritoneal contamination with polymicrobial (aerobic and anaerobic) flora from the bowel or vagina may occur during surgery or as a result of trauma, septic abortion, or perforating diseases such as appendicitis.

Clinical signs in the acute phase include increasing abdominal tenderness and fever. Bacteremia, which may progress to septic shock, occurs fairly frequently. In female pelvic infections, bacteremia and septic pelvic thrombophlebitis are always a threat because of the rich vasculature of the female pelvis.

Initially, antimicrobial therapy directed against aerobes such as *Escherichia coli* often results in defervescence and clinical improvement. Failure of the patient to respond or recurrence of symptoms may indicate anaerobic involvement. *B. fragilis* is the anaerobe most frequently isolated in patients with intra-abdominal sepsis or serious female pelvic infections.

© 1978 The Upjohn Company

Late Phase:
Peritoneal Response

The clinical course may progress to walling off of the infection and subsequent abscess formation. These collections of pus can be located intraperitoneally, retroperitoneally, or within the viscera.

Progression from peritonitis to abscess formation may be an insidious process or may be marked by sudden deterioration of the patient who had been recovering. At this point, failure to respond to appropriate antibiotic therapy should alert the clinician to the possibility of intra-abdominal or pelvic abscess formation and generally the dominant pathogens; the coexistent anaerobes may contribute to the clinical picture. In the patient who progresses to the late phase and develops an abscess, anaerobes (especially *Bacteroides fragilis*) are the dominant isolates.

the potential need for operative intervention.

In both the early peritonitis stage and the later abscess stage, culture of purulent material yields aerobes and anaerobes in the majority of instances. In fact, anaerobes have been isolated from 90% to 96% of intra-abdominal infections associated with bowel perforation. Anaerobes such as *B. fragilis* have been isolated in 80% to 100% of patients with pelvic abscesses studied with appropriate techniques of specimen collection and culture.

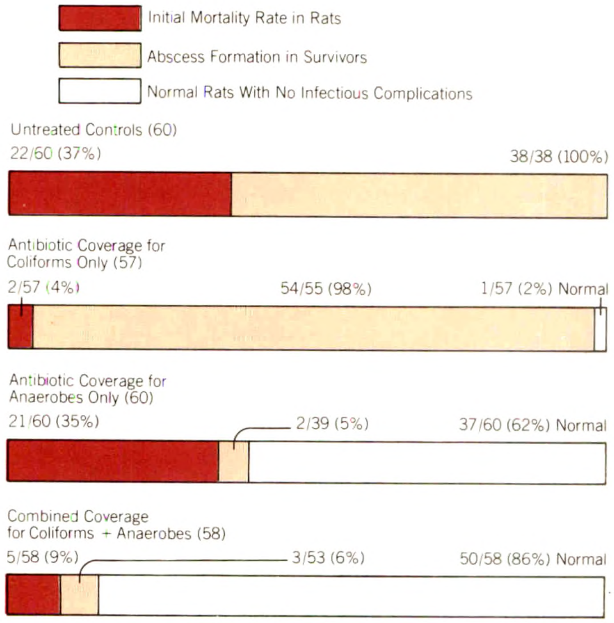
For information about one antibiotic to consider in treating serious infections due to anaerobic pathogens, please turn the page.

Upjohn

INDUCED PERITONEAL SOILAGE

The sequence of events that follow experimental induction of peritoneal soilage in rats parallels the biphasic course of this disease. Although animal data cannot be directly applied to humans, this model helps explain the pathogenesis.

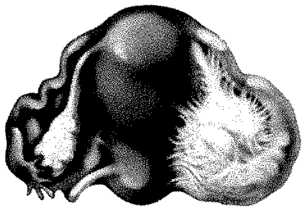
A standardized inoculum of rat colonic contents containing both aerobic and anaerobic organisms was implanted into the peritoneal cavity of male Wistar rats. The animals were observed for response and survivors were sacrificed after ten days. The rats developed a two-stage disease: initial, acute peritonitis and later, intra-abdominal abscesses. Mortality and progression of these stages varied sharply with antimicrobial coverage for aerobes, anaerobes, or both.

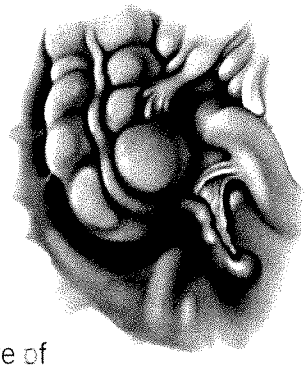


In this study, coliform organisms appeared to be responsible for the early mortality associated with fecal peritonitis, whereas *B. fragilis* and other anaerobes were associated with later abscess formation.

Upjohn

THERAPEUTIC CONSIDERATIONS...





Anaerobic activity

Cleocin® PO$_4$ (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal and female pelvic infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection; serious lower respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; and serious skin and soft-tissue infections caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, in vitro dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO$_4$ in gram-positive infections has been investigated both clinically and bacteriologically. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Indications include: serious lower respiratory tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances, the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible in vitro and were successfully eradicated from the clinical lesions.

Other therapeutic considerations

1. Cleocin PO$_4$ (clindamycin phosphate injection) is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO$_4$ is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Cleocin PO$_4$ can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO$_4$ should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO$_4$ should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section of the brief summary on the following page.

> If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

---

*Clostridia are more resistant than most anaerobes to clindamycin. Some species, eg, *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative. MED B-5-S J-6219-9

STERILE SOLUTION – FOR INTRAMUSCULAR AND INTRAVENOUS USE

Cleocin® Phosphate

(clindamycin phosphate injection, N.F.)

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

When the need for injectables is over...help keep your patient free of opiates, relieve pain.

Potent - Dependable - Nonopiate

Talwin® HCl 50 mg.

brand of pentazocine HCl tablets, NF

equivalent to 50 mg. base

Relieves pain as well as 60 mg. of codeine.

MILD ANALGESICS OFTEN DON'T WORK:

In a double-blind single dose study involving 225 adult inpatients, the comparative efficacy of 650 mg. aspirin, 65 mg. dextropropoxyphene, and 50 mg. pentazocine for relief of postoperative pain was recorded.[1]

- All patients were suffering from moderate or severe pain.
- Pregnant women as well as patients with known renal, respiratory, cardiac, or hepatic insufficiency were excluded.
- The onset of action of pentazocine was rapid.
- Although aspirin, dextropropoxyphene, and pentazocine produced significant relief from pain, pentazocine was significantly more effective at a half hour.
- Side effects were recorded for 16 patients: in the aspirin group 2 patients complained of drowsiness and 1 of dizziness. In the dextropropoxyphene group 5 patients vomited and 3 patients complained of drowsiness or dizziness, while 5 patients who had received pentazocine complained of dizziness.
- Pentazocine should be an oral analgesic of choice for treatment of postoperative pain.

Opiates are too addictive, too restrictive:

"Despite their potent analgesic action, the morphine-like analgesics have disadvantages that limit their usefulness: respiratory depression, nausea, vomiting, constipation, cardiovascular effects (hypotension, bradycardia), histamine release, and in some patients, an increase in intracranial pressure. Other adverse reactions include miosis, spasm of the biliary and urinary tracts, and rarely, hypersensitivity phenomena (urticaria, rash, and anaphylactic reactions). Frequent repeated use produces psychic and physical dependence."[2]

Oral Talwin shows infrequent occurrence of certain adverse effects as:

- Severe respiratory depression
- Hypotension
- Constipation
- Urinary retention
- Tachycardia

Among RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions—hallucinations (usually visual)—have cleared spontaneously within a period of hours. Withdrawal symptoms after prolonged use of Talwin for the relief of pain have rarely been reported, even when administration was abruptly discontinued. There have been a few reports of dependence with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

For Continuing Postsurgical Pain Control

Talwin® HCl 50 mg.

brand of pentazocine HCl tablets, NF

equivalent to 50 mg. base

1 or 2 tablets every three or four hours

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Nonopiate

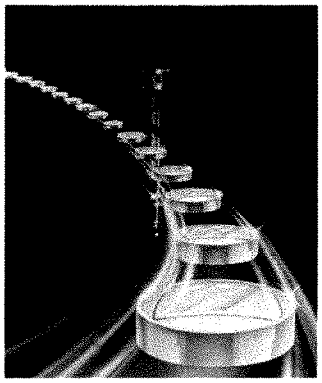
Talwin® HCl 50 mg.

brand of . equivalent to 50 mg. base

pentazocine HCl tablets, NF

Relieves pain of a moderate to severe nature.

Usual initial adult dose is 1 tablet every 3 or 4 hours.



Please consult full prescribing information before prescribing. A summary follows:

Talwin HCl is intended for the relief of moderate to severe pain. One 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. Talwin is a weak narcotic antagonist with sedative activity.

Contraindication

Hypersensitivity to pentazocine.

Warnings

Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin HCl should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions

Oral Talwin has been rarely reported to cause respiratory depression. It should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

Adverse Reactions

Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations; and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, paresthesia, toxic epidermal necrolysis.

Dosage and Administration

Adults: The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg. Tolerance is rare. Abrupt discontinuance following chronic use has rarely caused withdrawal symptoms.

Overdosage

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

References

1. Kay B: A clinical comparison of orally administered aspirin, dextropropoxyphene and pentazocine in the treatment of postoperative pain. *J Int Med Res* 2:149-152, 1974.
2. AMA Department of Drugs: *AMA Drug Evaluations*, ed 3. Littleton, Mass, Publishing Sciences Group, Inc, 1977, pp 327-328.

3096

Winthrop

Liver Resection in Children with Hepatic Neoplasms

JUDSON G. RANDOLPH, M.D.,* R. PETER ALTMAN, M.D.,† ROBERT M. ARENSMAN, M.D.,‡
MICHAEL E. MATLAK, M.D.,§ SANFORD L. LEIKIN, M.D.‖

In the past ten years, 28 patients with primary tumors of the liver have been treated. There were 11 benign tumors, including four hamartomas, three patients with focal nodular hyperplasia, and two each with congenital cysts and hemangioma. Hamartomas and masses of focal nodular hyperplasia should be excised when possible, but both are benign lesions; therefore life threatening excisions at the porta hepatis should be avoided. Cysts are often resectable, but when occupying all lobes of the liver, they can be successfully managed by marsupialization into the free peritoneal cavity. If resectable, hemangiomas should be removed; when occupying most of the liver as they often do, patients may be subject to platelet trapping or to cardiac failure. In some instances these lesions have been controlled by steroids, radiation therapy or hepatic artery ligation. Of 17 malignant tumors seen, 12 proved to be hepatoblastomas. Nine of the 12 patients underwent liver resection, of whom four are cured, (33%). There were three children with hepatocellular carcinomas and two with embryonal rhabdomyosarcoma. One child from each of these groups is cured by surgical excision. At present the only known cures in children with primary malignant liver neoplasms have been achieved by operative removal.

From the Departments of Surgery and Child Health, George Washington University Medical School, and the Surgical and Hematology/Oncology Service of Children's Hospital National Medical Center, Washington, D.C.

HEPATIC TUMORS IN CHILDREN represent grave clinical problems as well as technical challenges for the surgeon. Benign tumors usually have a satisfactory outcome in children and most of them may be allowed to remain in part or whole, if the removal will unnecessarily jeopardize the life of the child. Malignant tumors of the liver exact a heavy toll in the childhood age. Long-term survival has thus far not been influenced by chemotherapy, radiation therapy, or immunotherapy. At present, cure of primary malignant hepatic tumors is achieved only by complete surgical removal. The following report details the surgical experience in 28 children with hepatic tumors treated at the Children's Hospital National Medical Center from 1966 through 1976.

Clinical Material

There were 28 children in this series, eleven with benign tumors and 17 with primary malignancies (Table 1). Among those with benign disease, four presented with hamartoma at three days, seven months, eight months, and five years of age. There were three children with focal nodular hyperplasia, seen at three, four an one-half and eight years, respectively. Two patients, aged three months and two years, were seen with congenital cysts. There were two infants with hepatic hemangioma. There were none in this group with simple adenoma.

In the 17 children with malignancy, 12 with hepatoblastoma comprised the largest group. They ranged in age from one to 44 months at the time of diagnosis; eight of the 12 were under one year when first seen. Three of these children had pulmonary metastasis when first seen. As has been noted in other reports, the patients with hepatocellular carcinoma were older, appearing at three, eight and 12 years, respectively.[7] Two patients in the malignant group had embryonal rhabdomyosarcoma arising in the liver; these children were seen at 18 and 30 months.

Diagnosis

Liver tumors in children are usually discovered as asymptomatic abdominal masses. Fever, abdominal pain, anorexia and weakness are symptoms of advanced malignancy and are encountered in about 25%

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

[*] Professor of Surgery, George Washington University and Surgeon-in-Chief, Children's Hospital National Medical Center.

[†] Associate Professor of Surgery, George Washington University and Senior Attending Surgeon, Children's Hospital National Medical Center.

[‡] Chief Surgical Resident, Children's Hospital National Medical Center.

[§] Formerly Chief Surgical Resident, Children's Hospital National Medical Center.

[‖] Professor of Child Health, George Washington University and Director, Division of Hematology/Oncology, Children's Hospital National Medical Center.

Supported in part by United States Public Health Service Grant #CA03888.

0003-4932-78-0600-0599-0085 © J. B. Lippincott Company

TABLE 1. *Liver Tumors 1966–1976*

Hepatoblastoma	12
Hepatic cell carcinoma	3
Embryonal rhabdomyosarcoma	2
Mesenchymal hamartoma	4
Nodular hyperplasia	3
Congenital cysts	2
Hamangioma	2
	28

of children, many of whom have pulmonary metastases when first seen.[16] Anemia and thrombocytopenia are common findings but jaundice is rare. Alpha fetoprotein, a normal alpha globulin produced by embryonic hepatocytes, is a reliable biologic marker found in the serum of patients with hepatoblastoma.[1] Less frequently it is present in the serum of children with hepatocellular carcinoma. Alpha fetoprotein has usually disappeared from the serum of normal infants after a few months. The resynthesis of fetoprotein by the malignant hepatocyte is considered specific for these tumors, although it has been reported in the association with embryonal carcinoma of the testis and ovary.

The roentgenologic evaluation of the child presenting with an abdominal mass begins with plain films of the abdomen and intravenous pyelography. These studies identify renal and retroperitoneal lesions and may delineate encroachment of the tumor on adjacent abdominal structures. Ultrasonography aids in differentiating solid from cystic tumor masses. Hepatic imaging with radionucleides is useful in delineating the distribution of the tumor within the liver substances. The diagnosis is confirmed by hepatic angiography.[3,19] This definitive study is particularly useful to the surgeon because it will accurately define the arterial anatomy to the tumor and to the normal liver substance.

Treatment

Benign Disease

Several features in the handling of benign liver tumors are unique to the pediatric age group. Congenital cysts are usually detected in the early years of life. For some, a simple cystectomy or wedge resection is all that is required. Some of the cysts however, occupy the major portion of an entire lobe, necessitating formal lobectomy. If resection is not technically feasible, the cyst can be unroofed by excising the presenting surface. The edge of the remaining liver is secured with a running suture to marsupialize the cyst into the free peritoneal cavity (Fig. 1). It is not necessary to anastomose the open cyst to the gastrointestinal tract.

Hamartomas are not malignant tumors, but represent abnormal accumulations of normal tissue derived from the organ of origin.[2] Resection is the recommended treatment whenever technically feasible. Mass lesions representing focal nodular hyperplasia should be excised when surgically accessible.[27] Occasionally, these masses of hyperplastic tissue will appear grossly as malignant tumors, (Fig. 2) but they have no malignant potential.[24] When diagnostic confusion exists at the operating table, it is better to obtain a biopsy with frozen section, rather than to attempt a life-threatening excision for this benign lesion.

Hemangiomas of the liver become clinically apparent in several ways and therapy is directed accordingly.[6] Thrombocytopenia secondary to platelet trapping within the lesion, or congestive heart failure resulting from shunting in the tumor each necessitate intervention.[3,17] Surgical excision should be carried out whenever feasible, but if resection is not practical because of the location or extent of the tumor, or because there are multiple components present throughout the liver substance, alternative therapy is elected. Systemic steroids should be used in an effort to promote involution of the supporting connective tissue stroma of the hemangioma.[4,13,26] Radiation therapy may also be effective in reducing the tumor mass. Hepatic artery ligation has been shown to control the cardiac decompen-

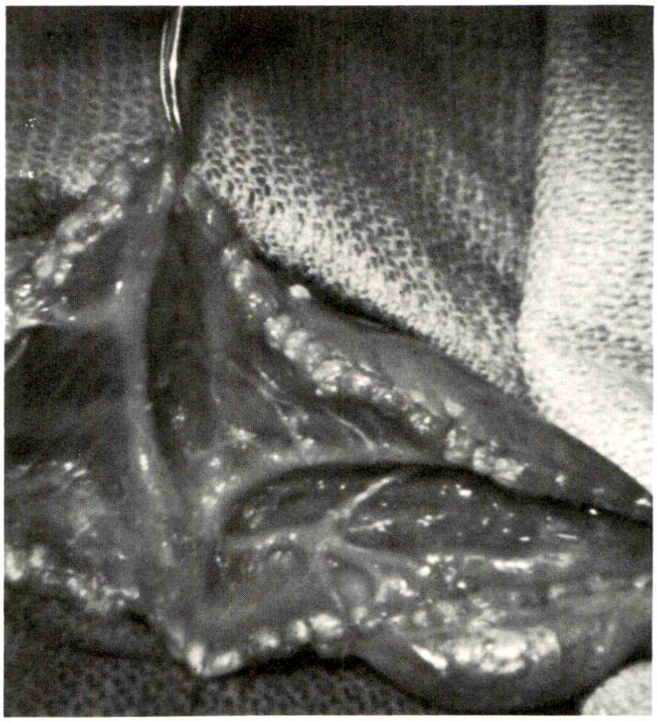


FIG. 1. Close up of the liver after resection of the anterior presenting portion of a congenital cyst. The edge has been whip stitched to marsupialize the cyst in the free peritoneal cavity. Note the internal architecture of the liver.

sation in some infants by reducing the arterial flow through the tumor.[19] The natural history of these lesions is spontaneous regression. Therefore in some patients, pharmacologic control of the cardiac systems may reduce or eliminate the need for hazardous surgery.

Malignant Tumors

At present, the only successful therapy is operative excision of all of the malignant growth. In the past, the presence of pulmonary metastases have countermanded a decision for surgical removal of the tumor. However, the well-being of the patient after removal of the large primary mass and the potential for control of metastases by Adriamycin[10] suggest that resection of the primary mass in the liver should be carried out except in terminal disease states. X-ray therapy of very large tumors has been recommended as a preoperative measure to reduce the size and enhance the operability of the tumor. We believe it unlikely that tumors can be removed from one lobe by irradiation and therefore, doubt that operability is truly altered. Large tumors can usually be as safely removed as smaller ones.

Technical considerations in liver resection. For maximum safety major hepatic resection implies the need for intraoperative monitoring, which includes arterial access for blood pressure and blood gases, central venous pressure, and Doppler flow sensor. Adequate quantities of type-specific blood, platelets and fresh-frozen plasma must be available in advance of surgery. Preoperative preparation includes review of the angiograms with formulation of a surgical plan based upon the vascular anatomy.

Adequate exposure for safe resection can be obtained through a generous transverse abdominal incision. For children, it is rarely necessary to enter the chest, even for resection of the largest hepatic tumors. Disseminated disease through both lobes is obviously not resectible; however, enormous lesions arising in one lobe often displace the other without invading it, or involvement of the adjacent lobe by contiguous spread is amenable to surgical resection. An aggressive surgical approach is encouraged. The first step in resection is the mobilization of the liver by dividing its ligamentous attachments to the abdominal wall and diaphragm. In smaller children, the liver can be displaced almost out by the abdominal cavity, providing access to the retrohepatic vena cava. Caution must be exercised since vena caval angulation may occur if the liver is mobilized too far anteriorly. A sudden fall in cardiac output and central venous pressure signifies the need to replace the liver into its normal anatomic position until hemodynamic stability returns.

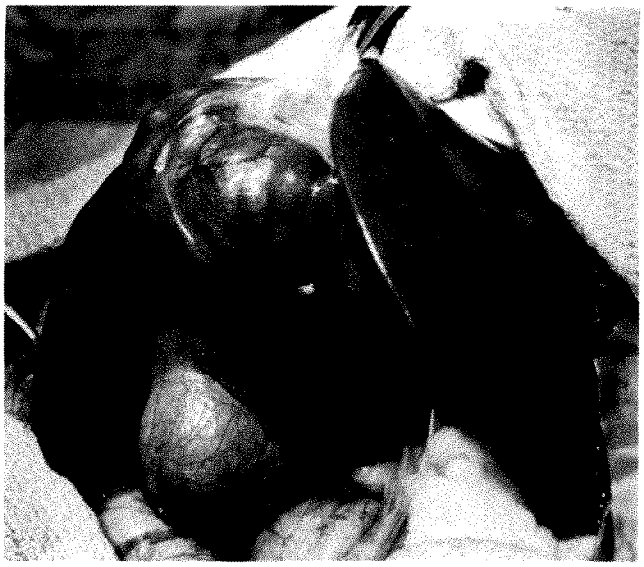


FIG. 2. Liver in 4½-year-old child with focal nodular hyperplasia. Note large veins on surface which resemble those seen in malignant tumors. This tumor was easily excised, but if located in the porta hepatis, such a tumor should be allowed to remain.

Routine canulation of the vena cava with an internal shunt is not advised, but appropriate tubes should be available should this maneuver be required in the event of catastrophic hemorrhage during dissection of the hepatic veins. These shunts can be placed from below the renal veins and passed upward to lie in the suprahepatic vena cava, or they can be inserted through the right atrium downward where, the canula is secured within the caval lumen below the liver.

Hepatic resection proceeds with isolation of the portal vein, common bile duct, and hepatic artery to the lobes and segments being resected. Extreme care must be exercised to protect the vascular and biliary structures to that portion of the liver which will remain.

Ligation of the hepatic veins is the most difficult and hazardous part of the resection. Particularly in infants, these veins are inaccessible, short and fragile. Avulsion or injury can result in serious hermorrhage. The middle hepatic vein is vulnerable to damage during either a right or a left lobectomy. The location of this vein should be established and the plane of resection planned to spare it. After securing the vascular and biliary structures, division of the liver substance remains to complete the resection. Several techniques, including finger fracture, knife handle dissection and sharp dissection have their proponents. We have used large vascular clamps to compress the liver substance at the line of resection. After the dissection is completed the clamps are applied along the line of proposed resection (Fig. 3). The large intersegmental ves-

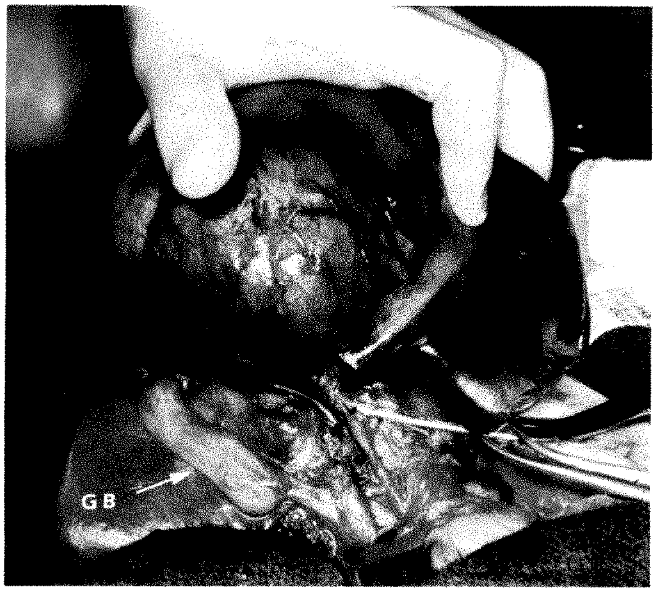


FIG. 3. Application of large aortic clamps, placed from above and below after the dissection has been completed.

sels and ducts are held securely by the clamps. These are subsequently suture ligated individually. Resection is thus expedited and blood loss minimized (Fig. 4). The area of resection is drained liberally.

After surgery the child is taken to the intensive care unit and monitored for postoperative fluid shifts, abnormalities of the clotting mechanism and electrolyte balance. Even after extensive hepatic resection, serum electrolyte and clotting factors are usually well maintained. Ten per cent glucose solutions are provided initially until glycogen stores are replenished. Hepatic regeneration proceeds rapidly, and biochemical parameters of liver function quickly return to the normal range even following the most radical resections.[20]

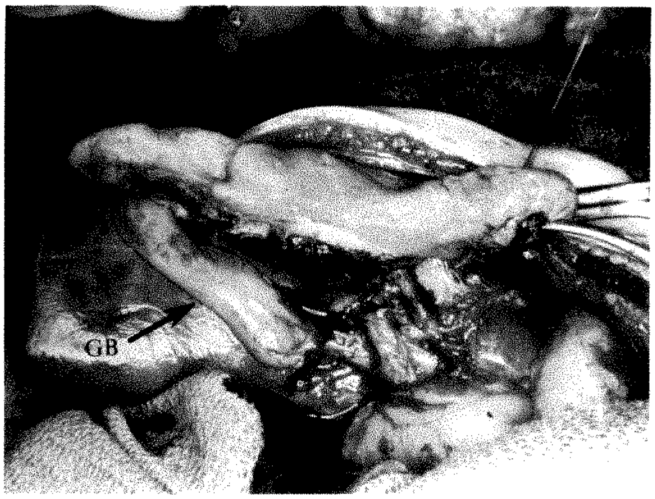


FIG. 4. Control of resection margin by large clamp after removal of tumor and left lobe.

TABLE 2. *Survival of Benign Liver Tumors*

	No.	Alive
Mesenchymal hamartoma	4	3
Nodular hyperplasia	3	3
Congenital cysts	2	2
Hemangioma	2	2
	11	10 (90%)

Postoperative radiation therapy is essential in rhabdomyosarcoma of the liver as is treatment with chemotherapy with Actinomycin, Vincristine and Cytoxan. There has, however, been no salutory effect on hepatoblastoma or hepatic cellular carcinoma by radiation therapy or chemotherapy.[14] A new protocol, developed by the Children's Cancer Study Group which employs Adriamycin, has yielded some encouraging early results.[10] At preset, the only hope for cure in children with hepatic malignancy lies in complete surgical extirpation of tumor. This can usually be accomplished and should be the surgical objective.

Results

Benign Tumors—Table 2

Eleven patients had surgery for benign liver tumors. There was one death. This occurred in a three day old baby who underwent right hepatic lobectomy for a mesenchymal hamartoma and succumbed to postoperative hemorrhage 24 hours later because of an uncontrollable coagulopathy. In the other three patients one had biopsy only because of an unresectable position in the porta hepatis; one had wedge resection and one had extended lobectomy.

There were three patients with focal nodular hyperplasia. One was treated successfully by lobectomy, one by wedge resection, and one who had biopsy only because of the location of the tumor in the porta hepatis.

Two patients had congenital cysts, one of whom was treated successfully by lobectomy. The other had extensive involvement of the liver substance by this cystic mass and therefore a marsupialization procedure was done. She remains completely well four and a half years after surgery. Both children treated for hemangioma had biopsy only. In one the hemangioma has been asymptomatic and the child is well. The other child had significant congestive heart failure which has been controlled by Digitalis. Radiation therapy and oral steroids administration has resulted in regression of the tumor.

Malignant Tumors

Hepatoblastoma. Of 12 children with hepatoblastoma nine have been treated with lobectomy. Three

TABLE 3. *Survival of Malignant Tumors*

	No.	Cured
Hepatoblastoma	12	4
Hepatic cell carcinoma	3	1
Rhabdomyosarcoma	2	1
	17	6 (35%)

patients, treated early in the series had pulmonary metastases at the time they were diagnosed and had biopsy only. Five of the nine patients subjected to lobectomy are surviving but one is known to have metastases. The other four are free of disease at two, two, three, and four years, respectively. The two year cure rate is 33%, and recurrence is unlikely in this group of very young patients.

Three patients had hepatic cell carcinoma. A 12-year-old child died shortly after biopsy with extensive pulmonary metastases. Another child underwent successful left lobectomy but died a year later with pulmonary metastases. An eight-year-old presented with multicentric carcinoma arising from a regenerative nodule in a liver with postnecrotic cirrhosis. Because of underlying liver disease, lobectomy was not practical. This patient has had three separate wedge resections. The unique biologic behavior of this tumor which characteristically recurs locally with pulmonary metastasis occurring rarely or only in terminal stages of the disease lends itself to treatment by limited local excision.

One of the two patients treated for rhabdomyosarcoma of the liver is alive and presumed cured by lobectomy. The other underwent combined lobectomy and Whipple operation but succumbed after two years from recurrent disease.

Discussion

This experience would seem to indicate that a therapeutic plan individualized for the patient on the basis of the histologic lesion is best for the management of children with benign hepatic tumors. Conversely, malignant disease can be successfully treated only by aggressive surgical resection. Since the original work by Quattlebaum in 1952[22] improvements in liver resection have been steadily seen over the past 25 years. Excision of a lobe of the liver or extended resection involving two of the major components of the liver are now standard operations.[5,9,11,15,18,21] Liver resection in children is easier in some respects than in adults; in particular, exposure, mobility of the organ, the elasticity of the surrounding viscera, and the parenchymal mass which must be traversed all make for a simpler technical operation. On the other hand, blood loss can rapidly plunge the small subject into shock. Therefore, precise monitoring, accurate blood replacement, and awareness of the child's vulnerability to cardiac arrest are all highly important facets of hepatic surgery in children. The use of clamps at the resection margin is controversial and can be complicated. We have felt them to be beneficial in these resections. They are not applied until after all dissection of the porta hepatis, the vena cava, and the hepatic venous outflow have been completed. Then we have used two simple large aortic clamps, one placed from above and one placed from below along the line of resection. This has minimized blood loss and provided control of the major vessels at the site of transection. The clamps are easy to remove and the operation has been safer with their use.

Because the location of benign tumors may be such that surgical resection may be impossible or unduly hazardous, an operative biopsy is recommended rather than proceeding with a life threatening resection which is not mandatory. Intraperitoneal seeding from operative manipulation or after rupture of hepatic tumors has not been seen in children's hepatic malignancies, so this deviation from cancer surgery principles is not unwise. Adenomas, hamartomas and focal nodular hyperplasia behave in a biologically benign fashion and all or any portion of these tumors can be allowed to remain *in situ*. However, when confined to a single lobe which lends itself to extirpation, resection of benign tumors is preferable because of possible symptoms or complications, such as encroachment on the surrounding viscera, bleeding or necrosis.

This series of patients confirms the view that surgical resection represents the only hope of cure for children with malignant liver disease. Vigorous surgical resection of rhabdomyosarcoma occurring in the liver and biliary system should be carried out even when the

TABLE 4. *Surgery for Liver Tumors*

	Biopsy (8)		Wedge (4)		Lobectomy (13)		Extended Lobectomy (3)	
Type	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Benign	4	0	3	0	2	1	1	0
Malignant	0	4	1	0	4	6	2	0

tumor is not completely accessible.[23] Improved survival for this lesion, in the liver as elsewhere in the body, has been realized with the addition of triple drug chemotherapy and radiation therapy. While chemotherapy has been disappointing for the management of primary hepatic tumors, current studies by the Children's Cancer Study Group suggest that Adriamycin may have a salutory affect on pulmonary metastases in some patients.[10] Therefore we would recommend surgical resection in the primary tumor even when pulmonary metastases have occurred as long as the patient is not in a terminal state.

A number of workers have spoken to the benefit of preoperative radiation, particularly because of its ability to shrink large tumors. However, there is no evidence that a tumor can be eliminated from a lobe of the liver into which it has grown. Therefore, the only beneficial affect of the radiation therapy is to shrink the tumor in size. It is our strong belief that large tumors can be handled safely and that radiation therapy is of little benefit in the preoperative phase. It has been well shown that radiation therapy after operation may damage the small amount of remaining liver after a major resection or may impede liver regeneration.[12,24] Therefore this modality must be used judiciously after liver resection in infants and children.

Conclusions

Complete excision of childhood malignant tumors of the liver has been possible in the majority of children in this series, resulting in a 35% cure rate. No benefit has been recognized from chemotherapy or radiation therapy in the children with hepatoblastoma or hepatic cell carcinoma. As in other locations, hepatic rhabdomyosarcoma is affected favorably by these adjunctive measures. Surgical approach to benign liver tumors should be individualized according to the type and location of the tumor.

References

1. Alpert, M. E. and Seeler, R. A.: Alpha Fetoprotein in Embryonal Hepatoblastoma. J. Pediatr., 77(6):1058, 1970.
2. Albrecht, E.: Ueber Hamartome. Verh. Deutsch Ges. Pathol., 7:153, 1904.
3. Berdon, W. E. and Baker, D. H.: Giant Hepatic Hemangioma with Cardiac Failure in the Newborn Infant. Value of High-dosage Intravenous Urography and Umbilical Angiography. Radiology, 92(7):1523, 1969.
4. Brown, S. H., Jr., Neerhout, R. C. and Fonkalsrud, E. W.: Prednisone Therapy in the Management of Large Hemangiomas in Infants and Children. Surgery, 71(2):168, Feb 72.
5. Clatworthy, H. W., Jr., Schiller, M. and Grosfeld, J. L.: Primary Liver Tumors in Infancy and Childhood. Forty-one Cases Variously Treated. Arch Surg., 109(2):143, 1974.
6. Dehner, L. P. and Ishak, K. G.: Vascular Tumors of the Liver in Infants and Children. A Study of 30 Cases and Review of the Literature. Arch. Pathol., 92(2):101, 1971.
7. Edmondson, H. A.: Differential Diagnosis of Tumors and Tumor-like Lesions of Liver in Infancy and Childhood. AMA J. Dis. Child., 91:168, 1956.
8. Ein, S. H. and Stephens, C. A.: Benign Liver Tumors and Cysts in Childhood. J. Pediatr. Surg., 9(6):847, 1974.
9. Ein, S. H. and Stephens, C. A.: Malignant Liver Tumors in Children. J. Pediatr. Surg., 9(4):491, 1974.
10. Evans, A. E., Tefft, M., Newton, W. and Randolph, J. G., unpublished data.
11. Exelby, R. P., Filler, R. M. and Grosfeld, J. L.: Liver Tumors in Children in the Particular Reference to Hepatoblastoma and Hepatocellular Carcinoma: American Academy of Pediatrics Surgical Section Survey—1974. J. Pediatr. Surg., 10(3): 329, 1975.
12. Filler, R. M., Tefft, M., & Vawter, G. F., et al.: Hepatic Lobectomy in Childhood: Effects of X-ray and Chemotherapy. J. Pediatr. Surg., 4:31, 1969.
13. Goldberg, S. J. and Fonkalsrud, E. W.: Successful Treatment of Hepatic Hemangioma with Corticosteroids. JAMA 208: 2473, 1969.
14. Holton, C. P., Burrington, J. D. and Hatch, E. I.: A Multiple Chemotherapeutic Approach to the Management of Hepatoblastoma. A Preliminary Report. Cancer, 37(4):1083, 1975.
15. Howat J. M.: Major Hepatic Resections in Infancy and Childhood. Gut, 12(3):212, 1971.
16. Ishak, K. G. and Glunz, P. R.: Hepatoblastoma and Hepatocarcinoma in Infancy and Childhood: Report of 47 Cases. Cancer, 20:396, 1967.
17. Levick, C. B. and Rubie, J.: Hemangioendothelioma of the Liver Simulating Congenital Heart Disease in an Infant. Arch. Dis. Child., 38:49, 1953.
18. Martin, L. W. and Woodman, K. S.: Hepatic Lobectomy for Hepatoblastoma in Infants and Children. Arch. Surg., 98(1):1, 1969.
19. Moss, A. A., Clark, R. E., Palubinskas, A. J. and Delorimier, A. A.: Angiographic Appearance of Benign and Malignant Hepatic Tumors in Infants and Children. Am. J. Roentgenol. Radium Ther. Nucl. Med., 113(1):61, 1971.
20. McDermott, W. V. Jr., Greenberger, N. J., Isselbacher, K. J., Weber, A. L., et al.: Major Hepatic Resection: Diagnostic Techniques and Metabolic Problems. Surgery, 54:5666, 1963.
21. Nikaido, H., Boggs, J. and Senson, O.: Liver Tumors in Infants and Children. Clinical and Pathological Analysis of 22 Cases. Arch. Surg., 101(2):245, 1970.
22. Quattlebaum, J. K. and Quattlebaum, J. K., Jr.: Technique of Hepatic Lobectomy. Ann. Surg., 149:648, 1959.
23. Soper, R. T. and Dunphy, D. L.: Sarcoma Botryides of the Biliary Tree. Surgery, 63(6):1005, 1968.
24. Sorensen, T. I. A. and Baden, H.: Benign Hepatocellur Tumors. Scand. J. Gastroenterol., 10:113, 75.
25. Tefft, M., Mitus, A., Das, L., et al.: Irradiation of the Liver in Children: Review of Experience in the Acute and Chronic Phases, and in the Intact Normal and Partially Resected. Am. J. Roentgenol. Radium Ther. Nucl. Med., 108(2):365, 1970.
26. Touloukian, R. J.: Hepatic Hemangioendothelioma During Infancy: Pathology Diagnosis and Treatment with Prednisone. Pediatrics, 45(1):71, 1970.
27. Whelan, T. J., Jr., Baugh, J. H. and Chandor, S.: Focal Nodular Hyperplasia of the Liver. Ann. Surg., 177(2):150, 1973.

Discussion

Dr. Jonathan A. van Heerden (Rochester, Minnesota): I rise briefly to bring to the attention of this group an instance which we recently encountered which we believe to be the first such incident recorded in the world's literature. Perhaps it isn't, and perhaps this group can tell us so.

We recently operated on a 4½-year-old girl with a large tumor of the right hepatic lobe. (Slide) This was a gigantic tumor, as seen here, which was a low grade hepatocellular carcinoma. The interesting thing about this was that at the time of right hepatic lobectomy, I could not find the portal vein. It's very difficult to lose the portal vein during a right hepatic lobectomy, but it was not to be found.

I therefore scrubbed out, and went a couple of rooms down the hall and found Dr. Adson, who is my hepatic surgery teacher, and told him the story: 'I can't find the portal vein.''

With a twinkle in his eye, he scrubbed out in a minute, and I could see him thinking that he would find this very soon. Well, he scrubbed in, and, indeed, there was no portal vein.

We found then by a little further dissection that the superior mesenteric vein entered the left renal vein, and hence into the vena cava, completely bypassing the liver. This was confirmed by postoperative angiography, which you can see here, that the superior mesenteric vein joined in two trunks to form a common trunk here, which on other films was joined by the splenic vein to then enter the left renal vein, and up the vena cava.

(Slide) Subtraction films show this, perhaps, a little bit better, where you can see this common trunk being formed by these two right here, and into the left renal vein and up the vena cava.

We called Dr. Starzl soon after this, and he was not aware of this ever occurring, to his knowledge. We called Dr. Henry Hollinshead, of anatomy textbook fame, who is now in North Carolina, and he came across this reference which was reported in the French literature of fetal monsters that died soon after birth.

The etiological and physiological implications of this anomaly are, of course, very interesting. Did this anomaly have anything to do with the formation of a hepatocellular carcinoma in a 4½-year-old girl? And secondly, are the hepatotropic factors, so often alluded to by Dr. Starzl, not in play in this young girl? For, indeed, if they were important for hepatocellular regeneration, then this girl's liver should not regenerate.

We operated on her just 5½ months ago, and her liver regeneration has proceeded along normal lines, and is almost double in size now.

I would greatly value Dr. Randolph's comments on this case.

[Corrected copy of Dr. Dennis W. Shermeta's discussion had not been received six weeks after mailing of the reporter's transcript, and is not included here.]

Dr. Judson G. Randolph (Closing discussion): I have recently come back from a visit to Australia; in Melbourne they showed me a very similar patient, and afterwards discussed several patients they have had with primary anomalies of the portal vein. I had not seen such a case before, and they had one case which was identical to this.

I do think the observation about the nutritional substrate being deprived from the liver initially, and yet there being good immediate growth of liver substance, is an important one.

I appreciate Dr. Shermeta's comments, and his calling our attention to gallium scanning, which is useful in some patients.

I know my friend Dr. Shermeta won't take offense if I disagree strongly with him, just to emphasize a point that we have made in this paper. In his own characteristic way, he has demonstrated another innovative technique with the introduction of a chemotherapeutic substance into the left hepatic artery. I think there could be danger with that, because of the possible spillback into other radicles of the hepatic artery; more importantly, I believe he would have achieved the same effect two months earlier if he had slipped a silk ligature around the left hepatic artery. It is my strong belief that the large, as well as small, tumors can be resected safely, if their anatomy will permit.

Abdominal Drainage Following Appendectomy and Cholecystectomy

H. HARLAN STONE, M.D., C. ANN HOOPER, B.A., B.S., R.N., WILLIAM J. MILLIKAN, JR., M.D.

Consecutive patients undergoing emergency appendectomy (283) or urgent cholecystectomy (51) were prospectively studied for the development of postoperative incisional or peritoneal sepsis. Severity of the original peritoneal infection was carefully recorded, while use of a Penrose dam to drain the peritoneum was randomized according to pre-assigned hospital number. Both aerobic and anaerobic cultures were taken from the abdomen at the time of operation as well as from all postoperative infectious foci. Results demonstrated no essential differences in incidence of wound and peritoneal infection following appendectomy for simple or suppurative appendicitis (187) or following cholecystectomy for acute cholecystitis (51). However, with gangrenous or perforative appendicitis (94), incisional and intra-abdominal infection rates were 43% and 45%, respectively, when a drain was used; yet only 29 and 13%, respectively, without a drain. These latter differences were significant ($p < 0.001$). In addition, intra-abdominal abscesses were three times as likely to drain through the incision than along any tract provided by the rubber conduit. Cultures revealed that hospital pathogens accounted for a greater proportion of wound and peritoneal sepsis after cholecystectomy and appendectomy for simple or suppurative appendicitis if a drain had been inserted than if managed otherwise. By contrast, a mixed bacterial flora was responsible for most infections following appendectomy for gangrenous or perforated appendicitis, irrespective as to use of a drain.

From the Department of Surgery, Emory University School of Medicine, Atlanta, Georgia

THE USE OF ABDOMINAL DRAINS following celiotomy for trauma or infection has been a moot issue throughout most of the past century, that is, ever since surgeons were no longer denied free access to the peritoneal cavity.[3,24] Despite a surgical literature replete with prestigious opinions and examples of both good and bad effects of drainage, little in the way of statistically valid and objective data is available upon which to base a sound judgement.[20] Indeed, it has been unfounded or poorly construed theory, as tempered by an individual's own inconsistently recalled experiences, that has dictated the indications for insertion of a peritoneal drain. For example, until he became convinced that drains were at times necessary adjuncts to certain operations within the abdomen, Halsted himself was a strong advocate of uniform primary wound closure without drainage.[3]

In order to provide a more reliable guide to the use of a peritoneal drain, a prospective randomized clinical trial was outlined so as to study patients with chemical peritonitis occasionally progressing on to an aerobic gramnegative infection (acute cholecystitis), early aerobic bacterial peritonitis (simple and suppurative acute appendicitis), and more advanced mixed aerobic–anaerobic bacterial peritonitis (gangrenous and perforated acute appendicitis). In addition, all clinical evaluations were made not just on subjective interpretations of wound status, but also on objective bacteriologic data obtained at initial operation as well as from all subsequent infection-related complications. Final conclusions were then drawn only from statistically proven and thus true differences.

Design of Study

Between September 15, 1975 and November 15, 1977, all patients on the Trauma and Pediatric Surgical Services of Grady Memorial Hospital with a later surgically proven diagnosis of acute appendicitis or acute cholecystitis became candidates for study. Just prior to closure of the abdominal incision, a Penrose drain was inserted through a separate stab wound if the final digit of the patient's hospital number (previously assigned on a random basis by a hospital admissions clerk) was an odd figure. An even final digit dictated exclusion of any form of peritoneal drainage.

Drains were routinely protected by sterile disposable ileostomy bags placed so as to isolate the stab wound and to collect all fluid that might be discharged.[21] Bag changes and drain advancement were carried out under aseptic conditions. Drains were left in place for a minimum of five and a maximum of ten days.

The operative diagnosis of acute cholecystitis was

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Reprint requests: H. Harlan Stone, M.D., Department of Surgery, Emory University School of Medicine, Atlanta, Georgia 30303.

0003-4932-78-0600-0606-0085 © J. B. Lippincott Company

not further categorized. However, appendicitis was classified into one of four stages.[22] *Simple*: appendiceal edema and hyperemia with at most a thin, cloudy exudate. *Suppurative*: an indurated appendix covered, at least in part, by a purulent exudate and with cloudy peritoneal fluid. *Gangrenous*: a suppurated appendix with one or more areas of gangrene in the appendiceal wall. *Perforated*: gross perforation of the appendix with a purulent peritoneal exudate.

Both aerobic (brain–heart infusion broth) and anaerobic (cooked meat broth with a reducing agent) cultures were taken of the peritoneal cavity immediately upon abdominal entry at the time of operation. These were then placed in an incubator at 37° within two minutes of inoculation. All subsequent wound, intraabdominal, and drain tract infections were similarly cultured. Diagnosis of such infectious complications were based upon the presence of pus and a positive bacterial culture.

Routine aerobic isolation and identification methods were employed, while anaerobes were handled according to techniques outlined in the *VPI Anaerobe Laboratory Manual*.[13] Only aerobic isolates were tested for antibiotic susceptibility, with standard disc and tube dilution procedures being used.

Parenteral antibiotics were uniformly administered to all patients with a preoperative assumption or a surgically proven diagnosis of acute cholecystitis and gangrenous or perforated acute appendicitis. As a general principle, antibiotics were never given to patients with simple or suppurative appendicitis, that is except for one or two preoperative doses in cases misdiagnosed as having progressed to the more advanced stages of gangrene or perforation. Clinical findings that indicated intravenous antibiotic therapy should be instituted preoperatively in patients with appendicitis were:[21] 1) a rectal temperature of 39° or greater; 2) generalized abdominal tenderness; 3) a white blood count equal to or greater than 14,000/mm^3; and 4) an onset of symptoms more than 36 hours prior to admission to the hospital. Presence of any two or more of these criteria or a clinical diagnosis of acute cholecystitis always led to the administration of parenteral antibiotics during preoperative fluid resuscitation.

Parenteral antibiotic regimens were changed according to strict drug protocols twice during the study. Between September 15, 1975 and August 31, 1976, only the cephalosporin Cefamandole (20–25 mg/kg. body weight/6 hours I.V.) was administered to all patients warranting antibiotic therapy. From September 1, 1976 to April 30, 1977, the aminoglycoside Netilmicin (2 mg/kg/8 hours I.V.) was given. Finally, between May 1, 1977 and November 15, 1977, there was a randomization between Cefamandole (40 mg/kg/6 hours I.V.) and Gentamicin (1 mg/kg/8 hours I.V.) according to the *next to the last* digit in the hospital number. These parenteral antibiotics were continued postoperatively for five to 21 days. On stopping antimicrobial therapy, all patients were observed for an additional two days within the hospital to rule out the presence of sepsis having been masked by the antibiotic. Later follow-up was then obtained through visits to the outpatient clinic.

Complicating sepsis often demonstrated the need for a different antibiotic regimen, and such was generally implemented according to clinical course and previous antimicrobial agents given. Occasionally blood and/or wound cultures provided the necessary information to insure a more appropriate choice of second course antibiotics.

Additional follow-up was directed not only at detecting signs of complicating sepsis, but also to identify problems related to the surgical incision and the peritoneal drain, if present. Data collected from clinical observations and the bacteriology laboratory were then subjected to critical analysis and tests of statistical significance, especially in relation to postoperative infection, presence of a drain, pathologic diagnosis, and bacteria present in the complicating septic focus. The Fisher exact test was used to compare these proportions.

Results

After 26 months, 351 patients had undergone emergency appendectomy. Of these, 37 were associated with abdominal trauma, while 31 were performed after laparotomy for a presumed appendicitis revealed a normal appendix. Exclusion of these 68 cases without acute appendicitis left a total of 283 patients for study. Gross pathologic diagnoses of the stage of appendicitis encountered at the time of operation were: simple: 66 patients; suppurative: 123 patients; gangrenous: 32 patients; perforated: 62 patients. Four patients subjected to urgent cholecystectomy for some noninflamatory condition were also excluded for the same reasons. The 51 remaining patients with acute choleystitis were then retained in the study.

The average age for all patients was 26.4 years, with a range of four months to 93 years (Table 1). Males predominated barely by 171 to 163 females. There were 255 blacks and 79 whites.

Culture analysis confirmed previous findings that simple and suppurative appendicitis are primarily aerobic bacterial infections (Fig. 1). On the other hand, progression to gangrene and then perforation uniformly produced a mixed infection with symbiosis between aerobic gram negative rods and a multitude of different

TABLE 1. *Clinical Material*

	Appendectomy	Cholecystectomy
Patients	283	51
Average age (years)	23.2	44.3
Range (years)	0.3–82	15–93
Male	159	12
Female	124	39
Black	226	29
White	57	22

anaerobic species.[22] Cholecystitis, however, rarely had an anaerobic component to the infection.

The incidence of infection in the surgical incision was essentially the same, irrespective as to whether the peritoneum had or had not been drained in patients with acute cholecystitis and with simple or suppurative appendicitis (Fig. 2). Although the wound infection rate in gangrenous and perforative appendicitis was greater in those patients with peritoneal drainage, this difference was not statistically significant.

Of the 30 patients with peritoneal drains and subsequent wound infections, ten or 33% had presumed nosocomial organisms as the cause, *i.e.*, *Beta hemolytic Streptococci*, penicillin-resistant *Staphlococcus aureus*, and *Pseudomonas aeruginosa*. (Table 2). By contrast, only two or 10% of the 21 patients not drained had such hospital-acquired pathogens participating in their wound infections. This difference in source of responsible bacteria between the two groups was significant ($p < 0.05$).

Many of the wound infections occurred in conjunction with intra-abdominal abscesses that appeared to have spontaneously discharged into the surgical incision and thus were often referred to as subfascial collections. Unfortunately, the exact frequency of this event could never be determined.

Extensive necrotizing infections of the abdominal wall developed in three patients, each of whom had been drained. In two, the drain tract appeared to be the original focus, while the surgical incision seemed to be the first area involved in the third case. Radical excision of abdominal wall in full thickness and reconstruction with prolene mesh were required in all three.[22] Two survived.

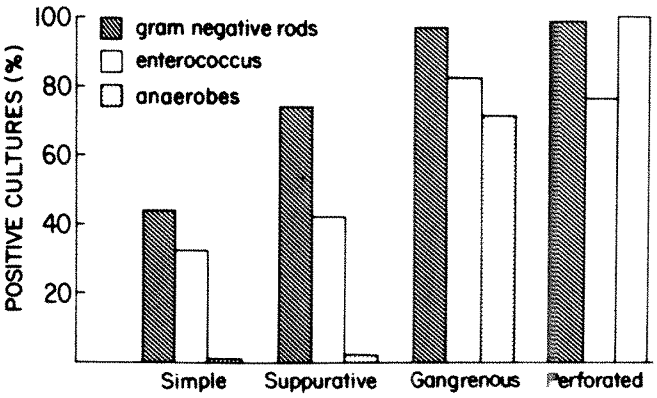


FIG. 1. Peritoneal cultures of acute appendicitis. Bacterial flora of the peritoneal fluid from patients with various stages of appendicitis.

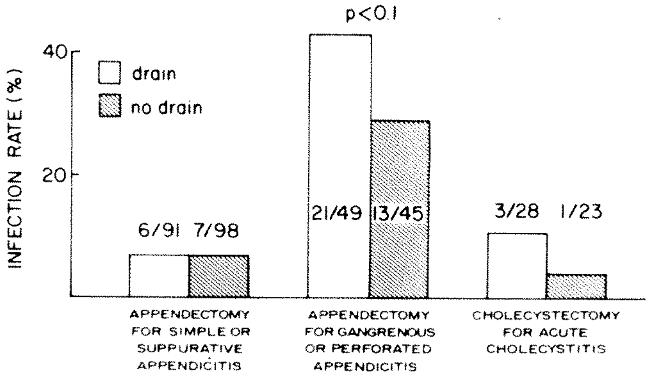


FIG. 2. Wound infection rates in the surgical incision.

Intra-abdominal abscesses rarely occurred following cholecystectomy and appendectomy for simple or suppurative appendicitis. There were no differences in incidence of this complication with respect to use or omission of a peritoneal drain. (Fig. 3). In gangrenous and perforative apendicitis, however, intra-abdominal abscess was a common complication. Transperitoneal drainage at the time of original operation in these cases produced an intra-abdominal infection rate (45%) that was significantly greater ($p < 0.001$) than if the drain had not been inserted (13%).

Cultures revealed that only one of the nine patients not drained who later developed an intra-abdominal infection had nosocomial organisms in the subsequent infecting flora (Table 3). Eleven of the 27 cases with a drain, however, had such hospital derived species

TABLE 2. *Cultures of Postoperative Wound Infections (Number of Patients with Positive Cultures)*

	Simple/ Suppurative Appendicitis		Gangrenous/ Perforated Appendicitis		Acute Cholecystitis	
Patients	Drain 6	No Drain 7	Drain 21	No Drain 13	Drain 3	No Drain 1
Beta streptococcus	1	—	1	—	1	—
S. aureus	1	1	1	1	2	—
Ps. aeruginosa	—	—	2	—	1	—
Other gram negative rods	5	6	19	12	1	1
Enterococcus	2	2	14	7	—	—
Anerobes	—	1	15	10	—	1

in their complicating intra-abdominal abscesses. Nevertheless, the difference in incidence, 11% versus 41%, was not statistically significant ($p = 0.1$) because of the small number of cases. If intra-abdominal infection rates due to nosocomial organisms were combined with similar figures for the surgical incision, then the results became highly significant ($p < 0.01$), for those drained had an incidence of hospital pathogens being responsible in 37% (21 of 57) verses a corresponding incidence of only 10% (three of 30) for patients not being so drained initially (Tables 2 and 3).

TABLE 3. *Cultures of Postoperative Intra-abdominal Infections (Number of Patients with Positive Cultures)*

	Simple/ Suppurative Appendicitis		Gangrenous/ Perforated Appendicitis		Acute Cholecystitis	
	Drain	No Drain	Drain	No Drain	Drain	No Drain
Patients	3	2	22	6	2	1
Beta streptococcus	1	—	—	1	1	—
S. aureus	2	—	3	—	2	—
Ps. aeruginosa	1	—	1	—	—	—
Other gram negative rods	1	2	19	5	—	1
Enterococcus	1	1	12	4	—	—
Anaerobes	—	—	14	6	—	—

Septic complications of the incision or within the abdomen in patients with a peritonitis caused by an aerobic bacterial flora, that is, in cases of acute cholecystitis and acute simple or suppurative appendicitis, had hospital pathogens as the predominant cause for their subsequent infections if a drain had been inserted (Tables 2 and 3). Nosocomial isolates represented 57% (13 of 23) of the bacterial species later recovered whenever a drain had been used at the first operation, while only 7% (one of 15) were hospital pathogens in the absence of initial drainage. These were significant statistically ($p < 0.01$). Data from mixed bacterial infections, however, as obtained with gangrenous or perforated appendicitis, revealed no such differences in complicating microbial flora.

When spontaneous abdominal drainage of an intra-abdominal collection of pus did occur through the right lower quadrant in 12 of the patients previously drained, in only three was the purulent discharge noted to exit via the drain tract. In each of the remaining nine, the surgical incision served as the drainage route.

Complications related to the surgical incision included two eviscerations and one dehiscence without bowel extrusion. One patient developed an early mechanical intestinal obstruction due to an adhesion to the healed peritoneal incision. This required reoperation six weeks following the first procedure.

Five fecal fistulas developed, and each occurred in a patient whose peritoneum had been drained at the time of appendectomy. One fistula persisted and eventually required right colectomy at a later date for final correction. As previously cited, the single death was due to an unremitting necrotizing fasciitis complicating the drain tract created at appendectomy for perforated appendicitis.

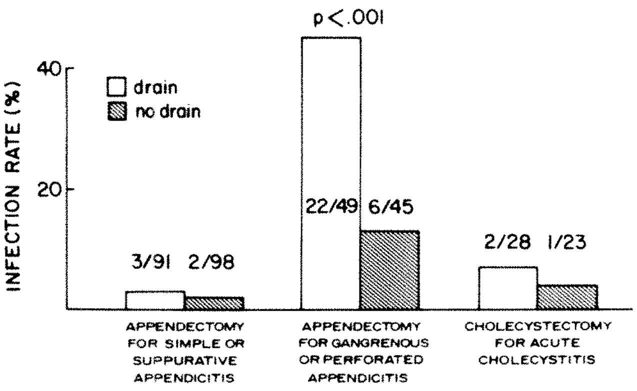


FIG. 3. Intraperitoneal infection rates.

Comment

Any drain, regardless of type, is a foreign body that maintains a fistulous communication between a given tissue plane or cavitary space and the external environment. By the drain's being a foreign body, local infection is always made a more likely consequence.[20] In addition, there is the threat of erosion into some adjacent structure, such as a major blood vessel or an intestinal suture line.[9]

While in place, the drain keeps tissues along the entire length of its passage separated and thereby will permit the egress of accumulated fluid and smaller particulate matter.[11,12,16,24] Nevertheless, the tract created is not a "one-way street;" for bacteria can migrate inward and colonize or supplant the microbial flora at the deepest extremity of the drain. It is for this reason that the superficial drain wound and that part of the drain exposed above the skin level must be assiduously protected from contamination until the drain has been completely removed.[5] Careful dressing techniques and use of the closed system provided by a skin-sealed sterile bag are important considerations.[21] Once the top most layers of the dressing have become saturated, bacteria can readily travel to the protruding drain and its site of skin penetration.

Dangers, especially with respect to infection, have been well documented for all forms of invasive treatment and monitoring. Recent surgical literature, however, has been more concerned with the indwelling urinary catheter and the intravenous cannula than with any method of wound or peritoneal drainage.[15,20] Nevertheless, the same potential for an infectious complication remains.

There have been few objective studies on the value or detriment of a drain placed in a superficial incision.[4-6,10,23] It does represent a form of delayed primary closure, which of itself can be quite useful in reducing the incidence of subsequent major sepsis in the heavily contaminated wound.[20,21] When the drain is situated no deeper that the external oblique fascia in cases of acute appendicitis, a reduction in incisional infection rate has been noted by some investigators.[6] Not withstanding, objective confirmatory studies do still seem to be warranted.

The benefits of peritoneal drainage have been repeatedly argued for many years.[3,24] Several case summaries, supporting each contention, have been recorded in the literature.[2-4,7,8,11,12,14,16-18,21,23,24] With instances of acute appendicitis, peritoneal drainage has appeared to be detrimental, as noted in the present study as well as in two other more recent reports. These have been well-designed, objective, randomized investigations and are in striking contrast to most other published accounts.[7,17]

Following cholecystectomy, only if the common duct has been incised or punctured has peritoneal drainage been deemed an absolute necessity.[3,8] Ross has reported good results in patients undergoing cholecystectomy in whom drains were not employed.[19] If blood removal is anticipated, however, as after splenectomy, infection is more likely to ensue whenever a peritoneal drain has been inserted.[2,18] Further, proximity of the drain to a functioning colostomy makes the risk as well as the seriousness of infection considerably greater.[21]

There appears to be a remarkable difference in the results of drainage according to whether it is used for a superficial wound or the peritoneal cavity. Drains do seem to offer some advantage in serving as a means of performing a delayed primary closure of the heavily contaminated superficial incision and for the escape of bile, pancreatic juice, and urine from the abdominal cavity proper. In addition, discharge of pus from an established abscess is always a valid indication, regardless of the site. In contrast, the drain by being a foreign body tends to disrupt suture lines, while blood clots and the more distant recesses of the peritoneal cavity are rarely if ever evacuated.

References

1. Bauer, A. W., Kirby, W. M. M., Sherris, J. C. and Tuck, M.: Antibiotic Susceptibility Testing By a Standardized Single Disc Method. Am. Clin. Pathol., 45:493, 1966.
2. Cerise, E. J., Pierce, W. A. and Diamond, D. L.: Abdominal Drains: Their Role as a Source of Infection Following Splenectomy. Ann. Surg., 171:764, 1970.
3. Crowe, S. J.: Halsted of Hopkins, Springfield, Charles C Thomas, 1957 p. 35.
4. Cruse, P. J. E. and Foord, R.: A Five-year Prospective Study of 23,649 Surgical Wounds. Arch. Surg., 107:206, 1973.
5. Drake, C. T., Goldman, E., Nichols, R. L., et al.: Environmental Air and Airborne Infections. Ann. Surg., 185:219, 1977.
6. Everson, N. W., Fossard, D. P., Nash, J. R. and MacDonald, R. C.: Wound Infection Following Appendicectomy: The Effect of Extra Peritoneal Wound Drainage and Systemic Antibiotic Prophylaxis. Br. J. Surg., 64:236, 1977.
7. Foster, G. E., Hardy, E. G. and Hardcastle, J. D.: Subcuticular Suturing After Appendicectomy. Lancet, 1:112B, 1977.
8. Goldberg, I. M., Goldberg, J. P. Liechty, R. D., et al.: Cholecystectomy With and Without Surgical Drainage. Am. J. Surg., 130:29, 1975.
9. Goldstein, H. S., Kredi, R., Cecil, F. and Wolcott, M. W.: Drains at the Suture Line. Surgery, 60:908, 1966.
10. Haller, J. A., Shaker, I. J. Donahoo, J. S., et al.: Peritoneal Drainage Versus Non-drainage for Generalized Peritonitis from Ruptured Appendicitis in Children; A Prospective Study. Ann. Surg., 177:595, 1973.
11. Hanna, E. A.: Efficiency of Peritoneal Drainage. Surg. Gynecol. Obstet., 131:983, 1970.
12. Hermann, G.: Intraperitoneal Drainage. Surg. Clin. North Am., 49:1279, 1969.
13. Holdeman, L. V. and Moore, W. E. C.: Anaerobe Laboratory Manual. VPI Anaerobe Laboratory, Blacksburg, Va. 1972.
14. Magarey, C. J., Chant, A. D. B., Rickford, C. R. K. and Margarey, J. R. Peritoneal Drainage and Systemic Antibiotics after Appendectomy. Lancet, 2:179, 1971.
15. McGowan, J. E., Jr., Parrott, P. L. and Duty, V. P.: Nosocomial Bacteremia: Potential for Prevention of Procedure-related cases. J.A.M.A. 237:2727, 1977.
16. Nora, P. F., Vanecko, R. M. and Bransfield, J. J.: Prophylactic Abdominal Drains. Arch. Surg., 105:173, 1972.
17. Norman, E., Korvald, E. and Lotveit, T.: Perforated Appendicitis—Lavage or Drainage? Ann. Chir. Gyn. Fenniae, 64: 195, 1975.
18. Olsen, W. R. and Beaudoin, D. E.: Wound Drainage After Splenectomy. Am. J. Surg., 117:615, 1969.
19. Ross, F. P. and Quinlan, R. M.: Eight Hundred Cholecystectomies. A Plea for Many Fewer Drains. Arch. Surg., 110: 721, 1975.
20. Stone, H. H.: Prophylactic measures for wound infections. *In* Varco, R. L., and Delaney, J. P. (eds.), Controversy in Surgery, Philadelphia, Saunders, 1976.
21. Stone, H. H. and Hester, T. R., Jr.: Incisional and Peritoneal Infection After Emergency Celiotomy. Ann. Surg., 177:669, 1973.
22. Stone, H. H., Kolb, L. D. and Geheber, C. E.: Incidence and Significance of Intraperitoneal Anaerobic Bacteria. Ann. Surg., 181:705, 1975.
23. Vakili, C.: Operative Treatment of Appendix Mass. Am. J. Surg., 131:312, 1976.
24. Yates, J. L.: An Experimental Study of the Local Effects of Peritoneal Drainage. Surg. Gynecol. Obstet., 1:473, 1905.

DISCUSSION

DR. ROBERT M. MILES (Memphis, Tennessee): I feel about Harlan Stone like E. F. Hutton. When he speaks, I listen, and I usually agree with him, and I agree with much of what he said today, but I'm concerned because some of his findings are at variance with some of the precepts that I have followed for many years; that is, routine drainage after cholecystectomy, and drainage after appendectomy for most cases of ruptured appendices, particularly in the presence of foreign bodies, such as a fecalith or necrotic tissue.

I have no collection of hard data to support an argument, but I do have vivid memories of problems that have occurred when drains were not used.

(Slide) This is such a case. She had a cholecystectomy elsewhere without drainage, and this x-ray was made about five days afterward and shows 2000 cc of bile which collected in the subphrenic and the subhepatic space.

Some years ago, in studying experimental bile peritonitis, we found that infection was usually the lethal factor, rather than the amount of bile; however, the amount of bile itself can kill, if it causes cholemia to the point of producing cardiac arrest and other problems. As we have seen from recent literature, the bile in about one third of the cases of acute cholecystitis is infected. Since infection is so important, it's always seemed to us reasonable to drain, so as to give an outlet to bile or blood and serum that may puddle in the subhepatic space and become infected.

I was glad that Dr. Stone commented on drainage and dressing technique, because they may be important factors in this connection. We use the subcostal incision for practically all of our elective cholecystectomies and for most of our emergency cholecystectomies, and we drain through the lateral extremity of the incision, not through a separate stab wound.

Of course, drains should be large enough, and they should afford as direct a route for drainage as possible. It should be remembered that the stuffing in a Penrose drain may obstruct, and the wound should not be closed too tightly about the drain, or it won't do its job.

We see that a number of these infections were due to hospital flora, which calls to mind the importance of wound dressing technique. Poor technique may account for introduction of hospital flora with resulting infection.

Recently, I received a telephone call at bedtime from a surgeon friend of mine in Arkansas, and he said, "Do you drain routinely after gallbladders?" And I said, "Yes." He said, "Well, I can't use you, then." And I said, "How come you can't use me?" And he said, "Well, I did one the other day, and didn't drain, and she developed a subhepatic abscess and peritonitis, and now they are suing me."

And so, in closing let me say that Dr. Stone has certainly given us something to think about.

Dr. Hiram C. Polk, Jr. (Louisville, Kentucky): Three times in the last five years Dr. Stone has presented before this group work that represented really landmark achievements in our understanding of surgical infection. I must say, however, to take Dr. Miles' analogy one step further, if that's E. F. Hutton, I'm going to take my $4.85 account to Merrill Lynch.

I really think that this presentation, while true in fact, is like so many of those exam questions you'll see on the recertification exam: They're sort of true, true, and not related.

I think Dr. Stone's emphasis upon the fact that a drain serves as a two way street and foreign body is absolutely correct. A lot of data of this sort is being presented at virtually every surgical meeting nowadays, forgetting the underlying principles, that drainage should be applied in certain circumstances and withheld in certain others. We're not talking about blanket application of drainage; we're talking about, in this case, the selective use of drainage.

What happens in this kind of study is that by draining lots of patients who didn't need it one distorts the comparison. For example, one would not drain a patient with acute appendicitis, without peritoneal fluid, and without a localized collection; you'd take that appendix out, and probably leave the wound open, and go about your business.

I think with the therapeutic foreign body you guarantee the emergence of hospital organisms. I believe, by the kind of study that Dr. Stone set up in this situation, he's led himself to a conclusion that probably isn't true in the widespread practice of surgery. It's absolutely true in this data, but I really fear these kinds of reports that are leading more and more surgeons to withhold drainage when there are lots of reasons to do it in a given circumstance.

As Dr. Miles presented, there are patients of that sort all around the country, because a surgeon once read that you don't need to drain after a gallbladder any more. These kinds of papers, as I say, while "true and true," are not really related to the clinical situation.

I have one serious misgiving about technical details. Dr. Stone, despite Dr. Warren's leadership, has been unable to move into the 20th century; there are relatively few surgeons any more who would use a passive drain of this sort. Most of us would depend on a suction drain, or do without. If you need it, you need the real thing; and a Penrose drain is a poor compromise for it.

Now, despite all this, I want to tell you that even the best hitters strike out every once in a while, and I think it was Stone's turn.

Dr. John W. Donald (Mobile, Alabama): I agree with Dr. Stone completely that drains should not be used following appendectomy for nonperforated appendicitis or for poorly localized peritonitis secondary to perforated appendicitis. I would like to comment briefly, though, on the use of a drain following cholecystectomy.

If one is draining for infection, the dominant indication is the rare case of perforated gallbladder and frank abscess, and I believe that Dr. Stone's findings have substantiated this point. On the other hand, I believe that a signal drain should be used following all biliary surgery. This drain is placed as a signal for possible bile leak or postoperative hemorrhage. We bring the drain out, as Dr. Miles does, through the lateral portion of the subcostal incision, or in the rare case of a midline incision, we bring it out through a stab wound in the right upper quadrant.

We remove this drain on the third postoperative day, and we believe that the early removal of the drain is extremely important in eliminating the danger of hospital-acquired sepsis.

I thought I would give briefly our experience with the use of a signal drain following cholecystectomy. By "our experience" I refer to the operations done by my brother, the late Dr. James Donald, and by me over a period of 25 years.

We have used such a drain on slightly more than 2000 consecutive biliary procedures, and to my knowledge, have had no complications from the use of the drain. We have been fortunate to have had no postoperative hemorrhage in these cases, but we have had considerable bile drainage from the drain site in four of these 2000 cases. We believe that this is usually from a small accessory biliary radicle in the gallbladder bed.

In three of these four cases, the drainage subsided after 24–48 hours, and then the drain was removed the following day. These three patients showed no signs of peritoneal irritation, and there was no morbidity.

The other case, which occurred 24 years ago, was an elderly lady who had common duct exploration with removal of stones and T-tube drainage in addition to cholecystectomy. Large quantities of bile drainage from the drain site were noted the night following the operation and continued. The T-tube placement was checked and seemed normal. Other late complications developed and the patient died. This patient should have been reoperated upon early, and I would recommend that if unexplained considerable bile drainage persists after 24–48 hours, reoperation should be strongly considered.

There are many surgeons who do not drain routinely following biliary procedures, and some would argue that since bile leak occurred in only four of 2000 cases in our series, perhaps a drain was unnecessary in 1996 cases. We do not believe that they are unnecessary. We still believe that a signal drain, if placed properly and removed early, does no harm, and can be helpful in the extremely rare instance of bile leak following biliary surgery.

Dr. Elmo J. Cerise (New Orleans, Louisiana): I have had considerable interest in this subject for a long period of time, and because I totally agree with what Dr. Stone has said and what he has shown us, and could almost totally disagree with the three previous discussants.

I think that, as I have studied this subject, drainage is seldom, if ever, indicated in the two types of conditions Dr. Stone described. I think a drain is only indicated when there is a specific collection to drain, and that oftentimes the most common drain used, which is the Penrose drain, is a source of infection, instead of benefit. And I think Dr. Stone has shown that.

There is now commercially available a far-from-ideal drain, but one which is a sump, and has a bacterial filter on it. I believe, however, that a so-called ideal drain could be constructed, and that it should be made of Silastic, or some other nonreactive material, that it should be a sump drain with an effective bacterial filter, that it should be highly polished, to prevent aggregation and debris formation, that it should be available in various sizes, and should be fairly economical.

I would like to ask Dr. Stone if, in those instances in which he believes a drain is indicated, what particular type of drain he now uses.

Dr. Francis C. Nance (New Orleans, Louisiana): I guess we probably ought not to see Penrose drains in New Orleans any more, because I can only agree with what Dr. Cerise has said, and I get up to support Dr. Stone in this study, and to point out to this audience that Dr. Stone has done what I would regard as a very difficult and very significant thing.

He's done a prospective and randomized study on this subject, and has come up with what I would regard as fairly definitive information.

I find it difficult to believe that he can persuade his residents to follow a protocol like that. I have a great deal of difficulty doing that with my own residents. But I think it's incumbent on those of you who are users of drains to come up with data that disagrees with this, because this is a prospective and a randomized study, competently carried out, and the data seems fairly clear to me.

So I think the monkey is on the back of the drainers, and I congratulate Dr. Stone for the information he has produced.

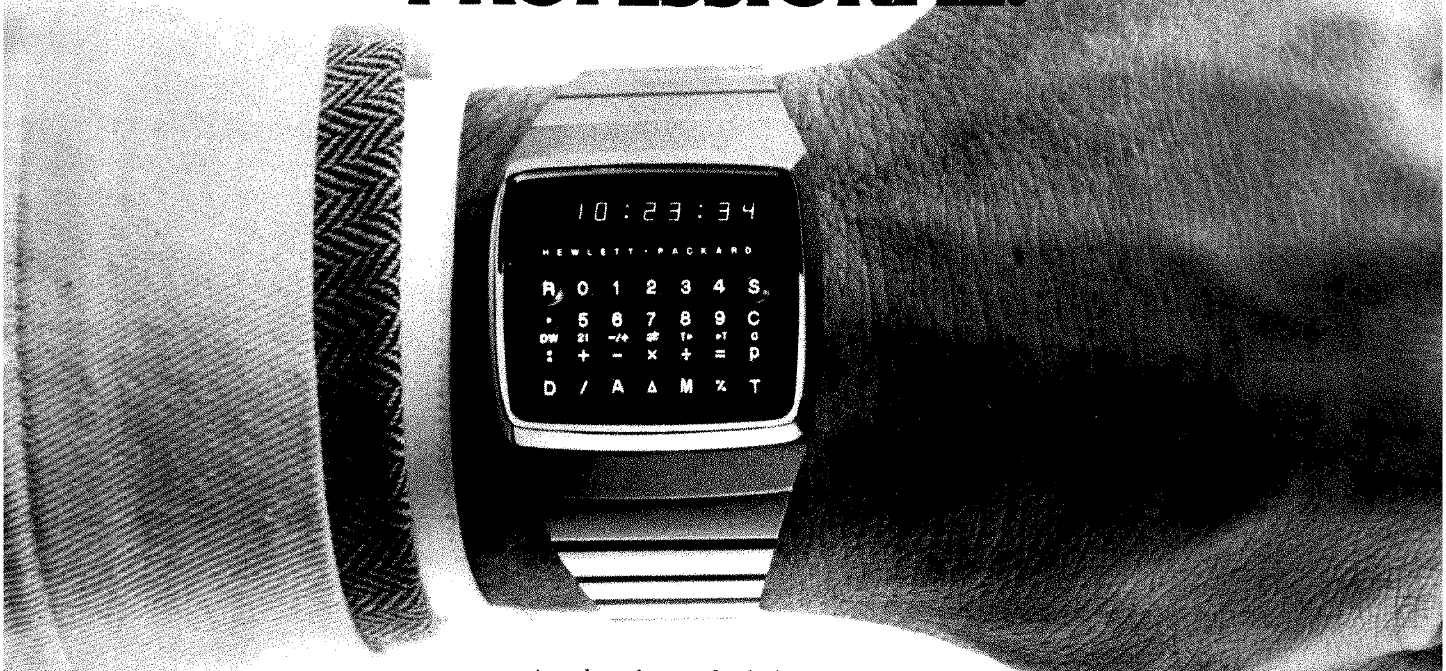
Dr. H. Harlan Stone (Closing discussion): First I would like to thank Dr. Miles and Dr. Donald for bringing out one important point: Drainage when one can anticipate the leak of bile. Following choledochotomy or a cholangiogram via the common duct, it's predictable. However, rarely does bile accumulate except in those cases.

Dr. Polk is absolutely correct in saying that the Penrose drain is a relatively archaic structure. The small suction drain is ideal, but not for longer than 24 hours.

Dr. Cerise, whose work on drainage following splenectomy was a stimulus to us, has brought out an important point: What type of drain should one use? Most of what we anticipate to drain will be liquid. Liquid does not flow uphill; and, therefore, we must use something that will overcome gravity. The sump is the only means we have available; that is, unless we routinely position our patients prone.

Finally, I want to thank Dr. Nance for his supportive comments. He did ask one critical question: Exactly how does one get residents to follow such a protocol? Whenever trainees are made to see the potential significance of a study, and if they are not forced to do the menial tasks, each and every one will be an energetic participant.

A REMARKABLE INSTRUMENT FOR THE MEDICAL PROFESSIONAL.



"I use it for calculating drug dosages and timing cardiac arrests where elapsed time is critical. It's always with me." Paul Hickey, M.D. Cambridge, Mass.

HP-01. A PERSONAL INFORMATION SYSTEM.

Here is perhaps the first wrist instrument that can become a professional instrument. The remarkable HP-01.

The HP-01 alone gives you the ability to interact various data: time, date, alarm/timer, stopwatch, calculator and storage memory.

How you use the HP-01 is limited only by your needs. And your imagination. The longer you own one, the more uses and applications you can expect to discover.

USE IT FOR WORK.

It is not surprising that many medical professionals have found a number of vital applications for their HP-01's:

"I use it to calibrate my pulmonary function equipment because of its accuracy to a hundredth of a second."
Ernest E. Musgrave, M.D., M.I.H
Paintsville, KY.

Another doctor finds his HP-01 invaluable to "time the rate of administration of cardiotonic and vasoactive medications given to critical patients in the Emergency Department."
John F. Davison, M.D.
Miami, FL.

Truly, with the HP-01, you have a professional instrument capable of meeting a broad spectrum of your professional needs. It can handle everything from basic math to calculating metric conversions.

It can remind you of an important call up to 100 hours in the future. And then tell you the number to call.

It can compute how much interest your money will earn in a 7-1/2% savings account versus a 6% tax-exempt bond. Or convert dollars to Deutsche marks—and Deutsche marks to yen.

In short, the professional applications are virtually unlimited.

AND FOR PLAY.

The HP-01 was not designed for business alone. It's meant to be thoroughly enjoyed.

So take it along to a road rally and clock precise time splits of the front runners. Take it sailing and use it to plot your course. When jogging, use it to pace yourself and clock your time for a mile. Or use it to calculate your biorhythms before today's tennis match.

IT'S LIKE NOTHING YOU'VE EXPERIENCED.

As you can see, the possible applications are virtually unlimited. That is why you should experience this remarkable instrument yourself. Visit your local dealer and ask for a demonstration. (For the address, **CALL TOLL-FREE 800-648-4711. IN NEVADA, 800-992-5710.**) Then you, too, may well agree with the words of one of your colleagues, "It's a beautiful instrument."

HEWLETT hp PACKARD

Dept. 660A, 1000 N.E. Circle Blvd. Corvallis, OR 97330

The HP-01 is now available in gold-filled case, stainless steel, or polished steel with matching bracelet or leather straps. Priced From $650.*
*Suggested retail price excluding applicable state and local taxes—Continental U.S.A., Alaska & Hawaii. 616/65

World Journal of Surgery

OFFICIAL JOURNAL OF THE SOCIÉTÉ INTERNATIONALE DE CHIRURGIE

Editor-in-Chief:
Marshall J. Orloff, M.D. • San Diego, U.S.A.

Editorial Board:
Marshall J. Orloff, San Diego, U.S.A. • Charles G. Clark, London, England • Horst Hamelmann, Marburg, Germany • Peter Heimann, Bergen, Norway • Jorge Puig La Calle, Barcelona, Spain • Rene Rettori, Paris, France • Jean Van Geertruyden, Brussels, Belgium

Consultants:
M. Allgöwer • E. Amdrup • S.-E. Bergentz • J.A. Borges D'Almeida • A. Diez • R.H. Egdahl • E.A. Elebute • D. Erlik • R.G. Favaloro • G. Fegiz • D.F. Aymerich • D. Gavriliu • J.D. Hardy • P. Kinnaert • P.J. Kuijjer • M.I. Kuzin • J. Lowenthal • L.D. MacLean • E. Malan • P. Malek • M. Mateos-Fournier • J.E. Murat • J.S. Najarian • G.B. Ong • S.R. Powers, Jr. • D.C. Sabiston, Jr. • S. Sakakibara • V. Schlosser • G.T. Shires • C. Solassol • V. Speranza • J.C. Thompson • E.J. Tierris • M. Trede • A.W. Wilkinson

WORLD JOURNAL OF SURGERY, *the official journal of the Société Internationale de Chirurgie, is a new publication designed to fill the need for rapid dissemination of new and important information about the science and art of surgery throughout the world. It is the only international journal covering the broad fields of surgery that contains refereed contributions of original work.*

WORLD JOURNAL OF SURGERY *rapidly publishes original articles that offer significant contributions to knowledge in the fields of clinical surgery, experimental surgery and related sciences, surgical education and the socioeconomic aspects of surgical care. Contributions are reviewed and selected by a group of distinguished surgeons from across the world who make up the Editorial Board and Consultants.*

In addition to original articles, each issue of the journal contains a unique feature titled "World Progress in Surgery." This special section presents a collection of invited contributions from recognized authorities on a single topic of current importance, organized under the direction of a guest editor. "World Progress in Surgery" provides an international readership with the latest, most authoritative information on major clinical problems in the fields of surgery.

WORLD JOURNAL OF SURGERY *is of interest and value to all surgeons. It is designed to offer contributors a world-wide audience and the broadest possible consideration of their work. It provides readers with critically reviewed, thoughtfully selected and up-to-date knowledge about advances in clinical surgery and the surgical sciences.*

SUBSCRIPTION INFORMATION
1978, Volume 2 (6 issues). Sample copies are available upon request.

North America
Personal rate: US $36.50 including postage and handling.
Institutional rate: US $52.50 including postage and handling.
Volume 1 (6 issues) 1977 is available at US $48.00 plus postage and handling.
Subscriptions are entered with prepayment only.

All other countries
US $63.00* or DM 156.10 including postage and handling.
Volume 1 (6 issues) 1977 is available at US $48.00 or DM 120.—plus postage and handling.
*Subscriptions are entered with prepayment only.

Please send your order or request to:

SPRINGER-VERLAG NEW YORK INC.
175 Fifth Avenue
New York, NY 10010 USA

or

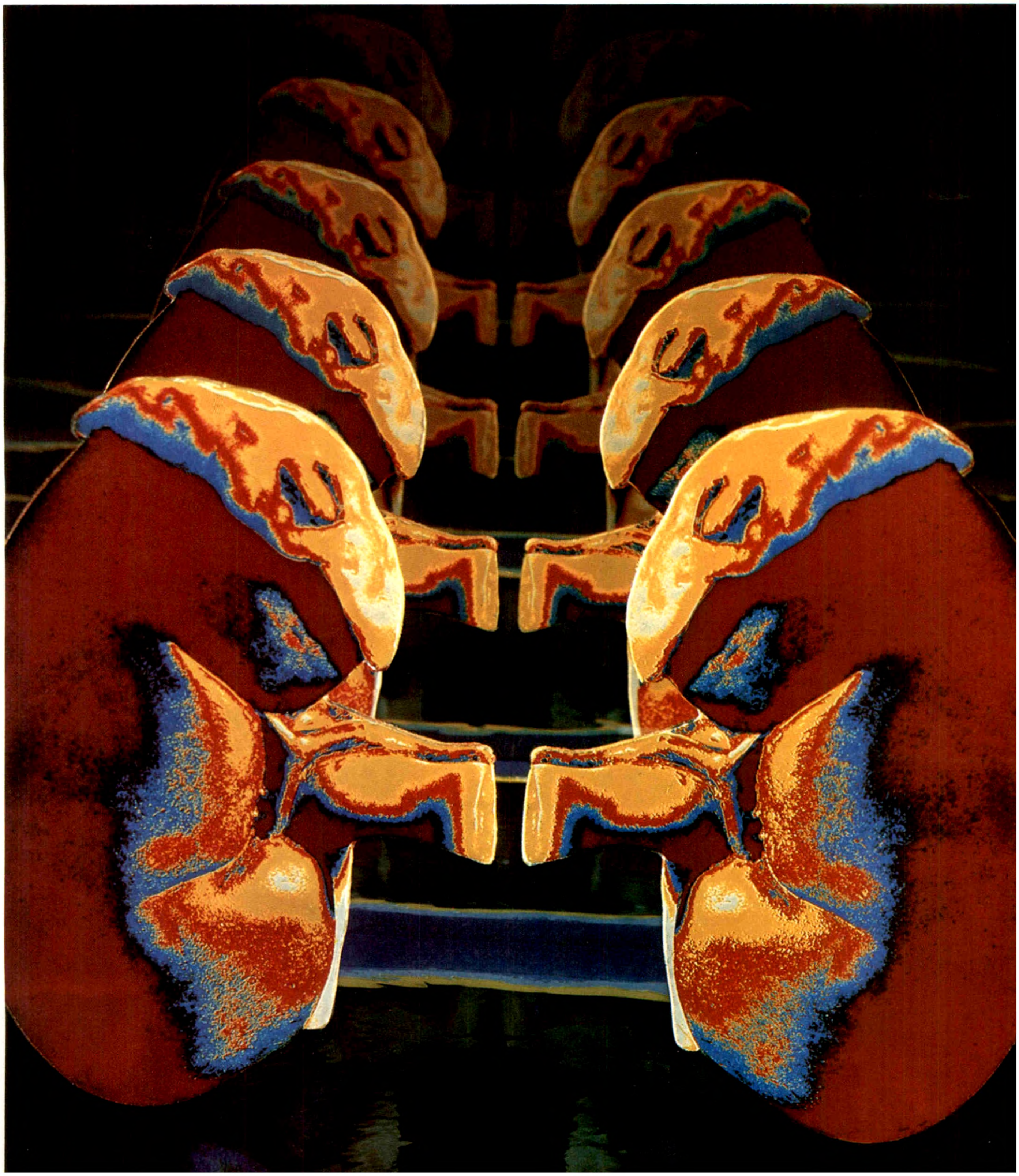
SPRINGER-VERLAG
Journal Promotion Department
P.O. Box 105280
D-6900 Heidelberg FRG

Membership in the Société Internationale de Chirurgie includes a subscription to this journal.

SPRINGER INTERNATIONAL

Now available the first amino acid injection indicated in acute renal failure

From McGaw, of Course



Nephramine™ (Essential Amino Acid Injection) helps meet the challenge of acute tubular necrosis

Product Description

Nephramine is a hypertonic, sterile, nonpyrogenic solution containing, in 250 ml, one and a half grams of nitrogen, Rose's recommended daily allowance of essential amino acids. A 250 ml container of Nephramine, when diluted with 500 ml of 70% dextrose in water, provides:

12.8 grams of essential amino acids

1190 nonprotein calories

750 ml volume

minimal electrolytes (less than 2 mEq of sodium)

Clinical Applications

Nephramine is indicated in the nutritional and therapeutic support of patients suffering from acute renal failure of various etiologies, especially when oral intake is impractical. It is given with hypertonic dextrose by central venous infusion. Candidates for Nephramine therapy include a variety of patients:

Those with acute tubular necrosis resulting from surgical or traumatic insult. In this category are hypovolemic conditions associated with severe hemorrhage, and trauma, including post-operative complications.

Pre- and post-operative dehydration.

Nephrotoxicity from microorganisms or exogenous agents.

Renal tubule insult without apparent disease or trauma.

Traditional enteral or parenteral feeding may be inadvisable in such patients because of gastrointestinal dysfunction, risk of azotemia, or difficulty of controlling fluid volume.

Potential Patient Benefits

Thorough clinical evaluations have shown that Nephramine, when properly administered to patients with reversible renal decompensation, will often:

reverse or minimize hyperkalemia

minimize elevation of serum concentrations of phosphorus and magnesium

decrease rate of BUN elevation

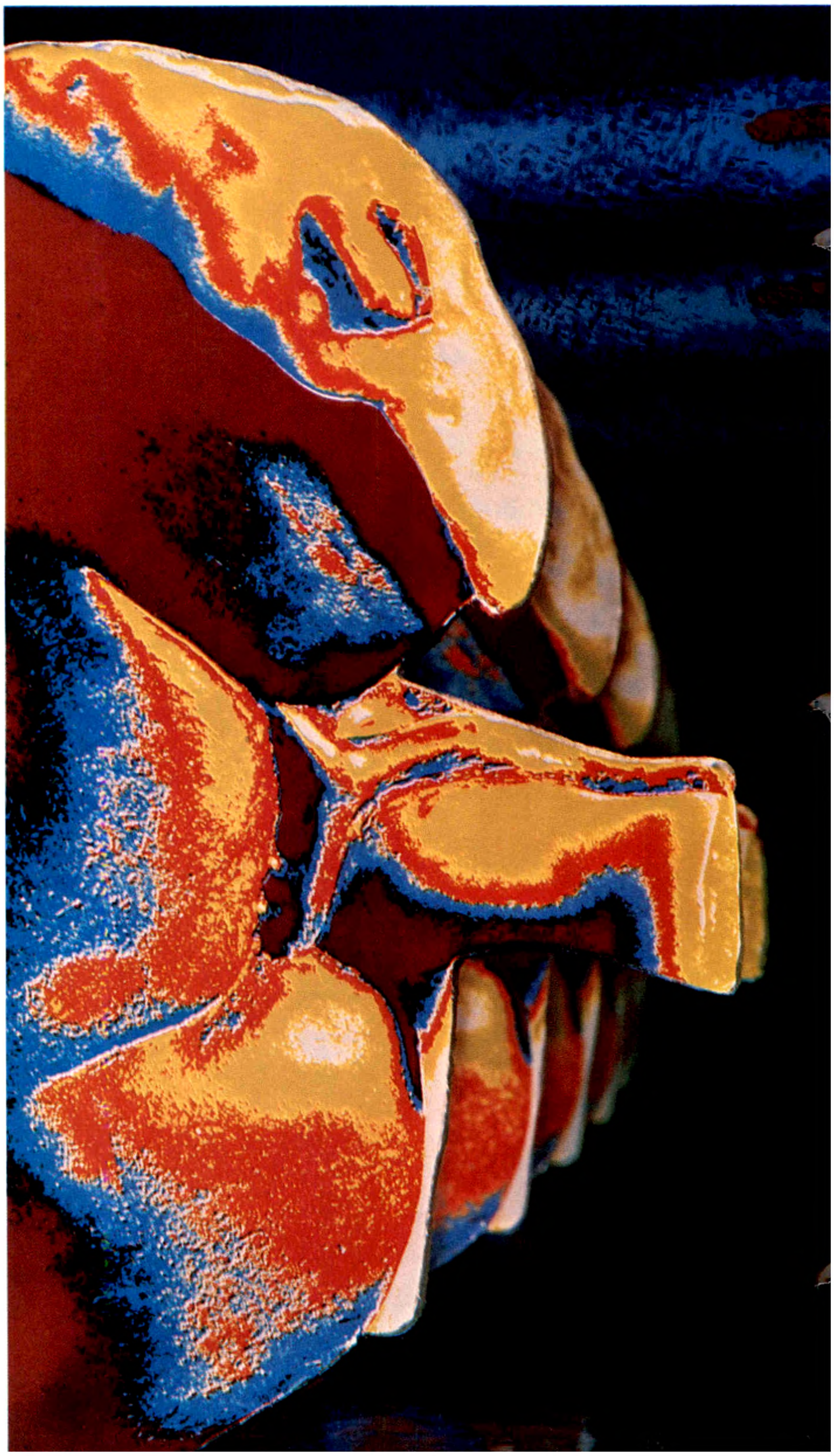
provide nutritional support for protein synthesis

promote an early return to renal function

decrease morbidity

Compatible With Dialysis

Nephramine does not replace dialysis. In most cases they may be administered concomitantly. Consult complete prescribing information for details.



McGaw
NEPHRAMINE™
(ESSENTIAL AMINO ACID INJECTION)
PROTECT FROM LIGHT PRIOR TO USE

Years of Investigation

Nephramine is an agent which has resulted from over 15 years of research. Beginning with the work of Rose and his associates, which established minimal quantities of eight amino acids required to maintain nitrogen equilibrium, Nephramine has been thoroughly studied. Controlled clinical evaluations have been conducted by leading clinical investigators. A selected bibliography follows:

Giordano C: Use of exogenous and endogenous urea for protein synthesis in normal and uremic subjects. *J Lab Clin Med* 62:231, 1963

Giovannetti S, Maggiore Q: A low-nitrogen diet with high biological value for severe chronic uremia. *Lancet* 1:1000, 1964

Dudrick SJ, Steiger E, Long JM: Renal failure in surgical patients. Treatment with intravenous essential amino acids and hypertonic glucose. *Surgery* 68: 180, 1970

Abel RM: Acute renal failure: treatment without dialysis by total parenteral nutrition. *Arch Surg* 103: 513, 1971

Abbott WM, Abel RM, Fischer JE: Treatment of acute renal insufficiency after aortoiliac surgery. *Arch Surg* 103:590, 1971

Leonard CD, Luke RG, Siegel RR: Parenteral essential amino acids in acute renal failure. *Urology* 6(2):154, 1975

Abel RM, Beck CH, Abbott WM, et al: Improved survival from acute renal failure with intravenous essential L-amino acids and glucose: Results of a prospective, double-blind study. *N Engl J Med* 288:695, 1973

Precautions

Special precautions should be taken with pediatric patients and those with renal insufficiency. Special care is necessary when administering hypertonic dextrose in glucose-intolerant patients, especially when receiving peritoneal dialysis. Insulin may be required to prevent severe hyperglycemia in those patients. Blood glucose should, therefore, be determined frequently.

Serum concentrations of potassium, phosphorus and magnesium should be monitored.

Laboratory and clinical monitoring of pediatric patients, especially when nutritionally depleted, must be comprehensive and frequent.

For prescribing information, see brief summary on following pages.

Copyright 1978 McGaw Laboratories

A

Nephramine™ (Essential Amino Acid Injection)

Before prescribing, see complete prescribing information in package insert or McGaw literature. The following is a brief summary.

Warning: Central venous nutrition therapy should be used only by those familiar with its administration and complications.

Protect From Light Until Use

Nephramine™
(Essential Amino Acid Injection)

Description

Contents per 100 ml

Essential Amino Acids (L-Lysine Acetate added)	5.1 g (12.8 g/250 ml)
Sodium Bisulfite	less than 0.05 g
Water for Injection USP	qs

pH adjusted with sodium hydroxide

Concentration of Electrolytes (mEq/liter): Sodium 6

Approximate concentration of amino acids:

	g/100 ml	g/250 ml
L-Isoleucine	0.56	1.40
L-Leucine	0.88	2.20
L-Lysine	0.64	1.60
(L-Lysine Acetate)	0.90	2.25
L-Methionine	0.88	2.20
L-Phenylalanine	0.88	2.20
L-Threonine	0.40	1.00
L-Tryptophan	0.20	0.50
L-Valine	0.65	1.62
Total Nitrogen	0.58	1.46

pH: Approx. 6.0

Calculated Osmolarity: Approx. 420 mOsm/liter

Do Not Use Unless Solution Is Clear and Vacuum Is Present

Nephramine is a sterile, nonpyrogenic solution containing crystalline essential amino acids. Each 250 ml unit provides Rose's recommended daily intake of essential amino acids.

Indications

Nephramine is indicated, in conjunction with other measures, for the management of potentially reversible renal decompensation, particularly when oral nutrition is unfeasible or impractical.

Contraindications

1. Severe uncorrected electrolyte and acid/base imbalance.
2. Hyperammonemia.
3. Decreased (subcritical) circulating blood volume.

Warnings

1. Safe and effective use of central venous nutrition requires a knowledge of nutrition as well as clinical expertise in recognition and treatment of the complications which can occur. FREQUENT CLINICAL EVALUATION AND LABORATORY DETERMINATIONS ARE NECESSARY FOR PROPER MONITORING OF CENTRAL VENOUS NUTRITION. Studies should include blood sugar, serum proteins, kidney and liver function tests, electrolytes, hemogram, carbon dioxide combining power, serum osmolality, blood cultures, blood ammonia levels, and circulating blood volume.
2. Nephramine does not replace dialysis and conventional supportive therapy in patients with renal failure.
3. Administration of Nephramine to children or low birth-weight infants, especially in high doses, may result in hyperammonemia.
4. Clinically significant hypokalemia, hypophosphatemia, or hypomagnesemia may occur as a result of therapy with Nephramine and hypertonic dextrose and replacement therapy may become necessary.
5. Administration of nitrogen in any form to patients with marked hepatic insufficiency or hepatic coma may result in serum amino acid imbalances, hyperammonemia, or central nervous system deterioration. Nephramine should, therefore, be used with caution in such patients.

Precautions

In order to promote urea nitrogen reutilization in patients with renal failure, it is essential to provide adequate calories with minimal amounts of the essential amino acids, and to severely restrict the intake of nonessential nitrogen. Hypertonic dextrose solutions are a convenient and metabolically effective source of concentrated calories.

Fluid balance must be carefully monitored in patients with renal failure and care should be taken to avoid circulatory overload, particularly in association with cardiac insufficiency.

Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

Special care must be taken when giving hypertonic dextrose to glucose-intolerant patients such as diabetic or prediabetic and uremic patients, especially when the latter are receiving peritoneal dialysis. To prevent severe hyperglycemia in such patients, insulin may be required.

Abrupt cessation of hypertonic dextrose infusion may result in rebound hypoglycemia.

Special Precautions of Central Venous Nutrition

Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure including solution preparation, administration, and patient monitoring. **It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team.**

Although a detailed discussion of the complications of central venous nutrition is beyond the scope of this disclosure, the following summary lists those based on current literature:

1. **Technical.** The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arterio-venous fistula, phlebitis, thrombosis, and air and catheter embolus.
2. **Septic.** The constant risk of sepsis is present du ing central venous nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of parenteral nutrition solutions and the placement and care of catheters be accomplish under controlled aseptic conditions.

   Parenteral nutrition solutions should ideally be p pared in the hospital pharmacy under a laminar flow hood. The key factor in their preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions a subsequent admixtures.

   Parenteral nutrition solutions should be used promptly after mixing. Any storage should be un refrigeration for as brief a time as possible. Administration time for a single bottle and set shoul never exceed 24 hours.

   Consult the medical literature for a discussion of the management of sepsis during central venous nutrition. In brief, typical management includes r placing the solution being administered with a fre container and set and culturing the contents for bacterial or fungal contamination. If sepsis persis and another source of infection is not identified, t catheter is removed, the proximal tip cultured, ar a new catheter reinserted when the fever has subsided. Nonspecific, prophylactic antibiotic treatment is not recommended. Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.
3. **Metabolic.** The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia ar glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo and hypervitaminosis, electrolyte imbalanc and hyperammonemia in children. Frequent clini evaluation and laboratory determinations are necessary, especially during the first few days of central venous nutrition, to prevent or minimize these complications.

   Administration of glucose at a rate exceeding the patient's utilization rate may lead to hyperglycem coma, and death.

Special Precautions in Patients with Renal Insufficiency

Frequent laboratory studies are necessary in patien with renal insufficiency due to underlying metabolic abnormalities. Hyperglycemia, a frequent complication, may not be reflected by glycosuria in renal failu Blood glucose, therefore, must be determined frequently, often every six hours, to guide dosage of dextrose and insulin if required.

Serum concentrations of potassium, phosphorus, ar magnesium may dramatically decline with successf treatment, individually or together; these substance should be supplemented as required. Special care must be taken to avoid hypokalemia in digitalized patients, or those with cardiac arrhythmias.

Special Precautions in Pediatric Patients

Nephramine should be used with special caution in pediatric patients, especially low birth-weight infant due to limited clinical experience. Laboratory and

clinical monitoring of pediatric patients, especially when nutritionally depleted, must be extensive and frequent. Initial total daily dose should be low, and increased slowly. Dosage of Nephramine™ (Essential Amino Acid Injection) above one gram of essential amino acids per kilogram body weight per day is not recommended.

Frequent monitoring of blood glucose is required in low birth-weight or septic infants as infusion of hypertonic dextrose carries a greater risk of hyperglycemia in such patients.

Nephramine contains no histidine, an amino acid considered essential for growth in infants. Long-term parenteral support of growing infants without provision of histidine intake is therefore inadvisable.

The absence of arginine in Nephramine may accentuate the risk of hyperammonemia in infants.

Adverse Effects
Infrequent instances of hyperammonemia have been reported following administration of essential amino acid solutions to patients with massive gastrointestinal hemorrhage, and non-uremic infants and children. Two pediatric patients with normal renal function received high doses of Nephramine and developed symptomatic hyperammonemia. In each case, serum ammonia levels decreased and clinical symptoms subsided when the infusions were discontinued.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

McGaw Laboratories
Division of American Hospital Supply Corporation
Irvine, CA 92714

FACULTY POSITION OPEN

College of Medicine, King Faisal University
Dammam, Saudi Arabia

PROFESSOR AND CHAIRMAN,
DEPARTMENT OF SURGERY

Applications are invited from U.S., British and Canadian surgeons with at least ten years teaching experience in a medical school. Opening is for September 1978; interviews scheduled with the Dean in the United States early in 1978. Language of instruction is English.

Salary and Benefits:

Academic Salary monthly in Saudi Riyals (SR)	*+ Clinical Bonus of 50%*	*= Total approximate annually in* U.S. dollars
SR 10,000	SR 5,000	$50,000

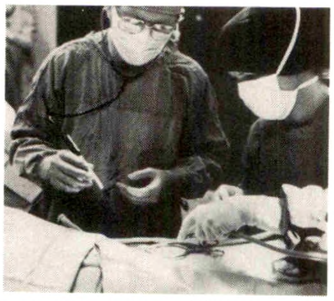
Free furnished accommodations and annual leave with travel allowance to country of origin for family of four. No Saudi income tax.

Send curriculum and references with addresses and telephone numbers to:

Mohammed T. Altorki, M.D., MRCP
Dean of the Medical Faculty
King Faisal University
c/o Saudi Arabian Educational Mission
2223 West Loop South, Suite 400
Houston, Texas 77027

Specify dates of teaching appointments and availability.

NEW MINIATURIZED DOPPLER

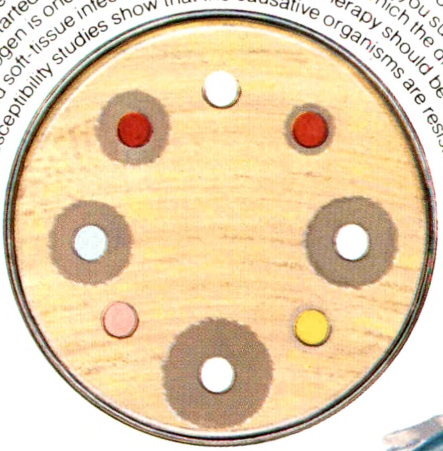


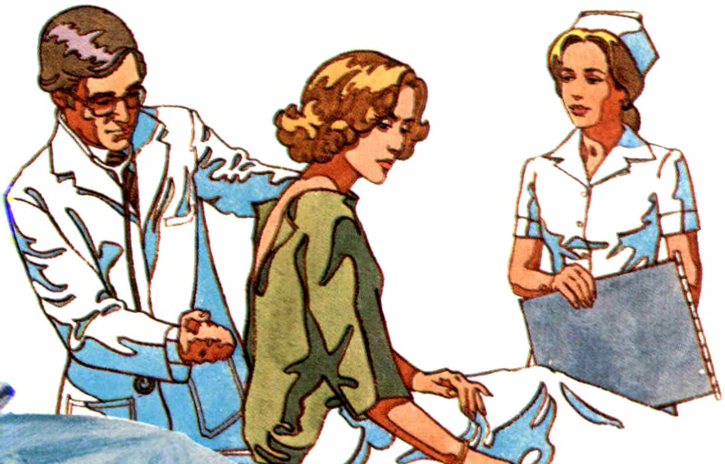
The Doplette® 10 portable Doppler probe is a completely self-contained pen-sized Doppler device that transforms a standard stethoscope into a tool with significant new diagnostic usefulness. Because the Doplette 10 can be gas sterilized, it becomes a valuable adjunct to the surgical suite. And, with shirt-pocket convenience and diagnostic capability, its versatility is extended to office, clinic or patient rounds for a wide variety of vascular applications. Includes batteries and cassette tape of typical Doppler sounds. For more information contact:

Physio-Control®

11811 Willows Road, Redmond, Washington 98052
206/883-1181, Cable: PHYSIO-RED, Telex: 32-0166

Appropriate cultures should be taken, but Keflin® (cephalothin sodium, Lilly) may be started before susceptibility results are obtained if you suspect the causative pathogen is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections.* Other antibiotic therapy should be instituted if susceptibility studies show that the causative organisms are resistant.

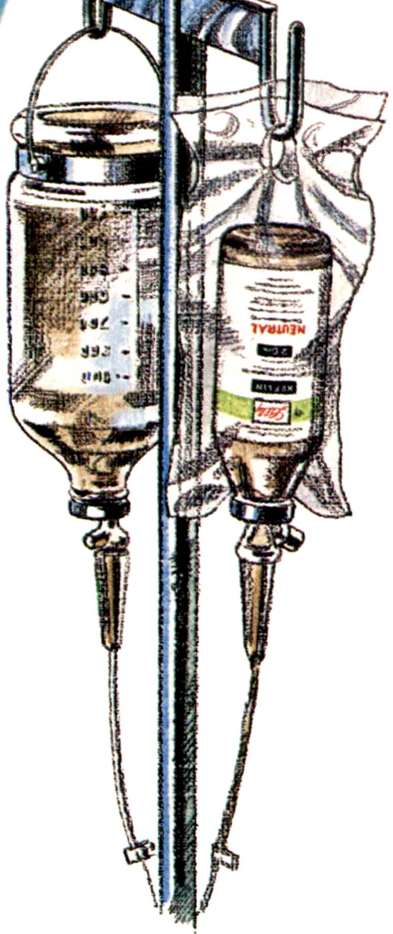


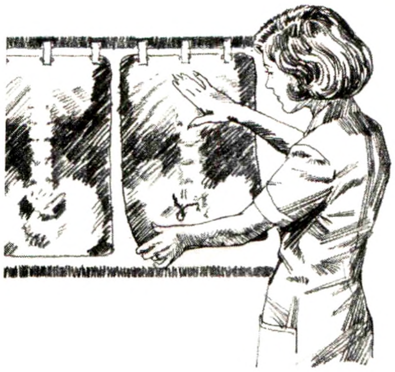


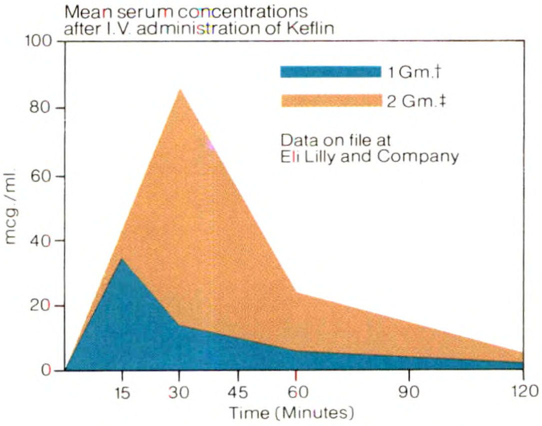
In the immunosuppressed patient, usual clinical signs and symptoms of infection may be missing or not clear. Hence, diagnosis and initiation of proper therapy become most urgent.

An initial loading dose of 1 to 2 Gm. of Keflin may be given regardless of the patient's renal status. Patients with impaired renal function should be placed on a reduced dosage schedule. Usual doses in such individuals may result in excessive serum concentrations.

Keflin may be administered I.V. or I.P. in dosages as high as 12 Gm. per day (in life-threatening infections).






Mean serum concentrations after I.V. administration of Keflin
1 Gm.†
2 Gm.‡
Data on file at Eli Lilly and Company
mcg./ml.
100
80
60
40
20
0
15
30
45
60
90
120
Time (Minutes)

† Administered to six patients by rapid I.V. infusion.

‡ Administered to ten patients over a thirty-minute period.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

Please see opposite page for summary of prescribing information.

In serious skin and soft-tissue infections*

OFTEN USEFUL WHEN MOST NEEDED

As you know, skin and soft-tissue infections,* including peritonitis, may progress with alarming rapidity in patients with impaired host defenses…even to the point of becoming irreversible. Keflin can often be useful before the infection becomes irreversible…exactly when it is most needed.

Eleven years after its introduction, Keflin continues to be effective against most strains of gram-positive and gram-negative organisms commonly implicated in serious skin and soft-tissue infections.* Therefore, when you suspect that the pathogen involved is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections,* you may begin therapy with Keflin even while results of susceptibility studies are pending…and thus save precious hours for the patient. Keflin may be administered to infants and to patients with reduced renal function.

Keflin should be given cautiously to penicillin-sensitive patients.

It is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Keflin®
cephalothin sodium
Neutral
for Injection
2 Gm.†
in 100-ml. ampoule

†Equivalent to cephalothin

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin* (cephalothin sodium, Lilly), Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy — Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape* (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. (111475S)

Additional information available to the profession on request

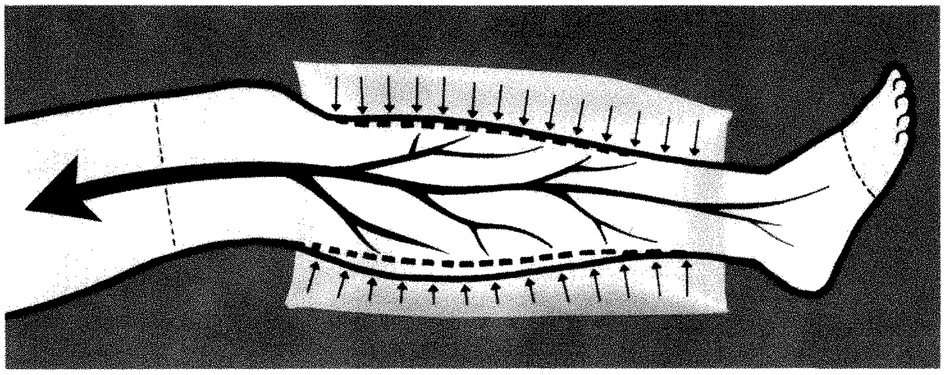
Lilly

Eli Lilly and Company
Indianapolis, Indiana 46206

600395

Up to 100,000 deaths from Pulmonary Embolism can be prevented

Now you can ambulate your patients on the table with the Venodyne ® intermittent compression system.



- ***Venodyne simulates calf muscle action.***
- ***Venodyne is totally non-invasive and non-pharmacologic.***
- ***Venodyne is simple to operate, compact, noiseless.***

Annually about 6,000,000 adults in the United States suffer from episodes of pulmonary embolization and the mortality rate is close to 100,000 per year.[1] The deep leg veins are the source of the embolism in most patients.[2] And two-thirds of the deaths from massive embolism have been considered to be potentially preventable.[2] Additionally, it has been estimated that 50% or more of patients presenting with venous thrombosis suffer from some form of post-thrombotic syndrome by 5 to 10 years after the thrombotic event[2].

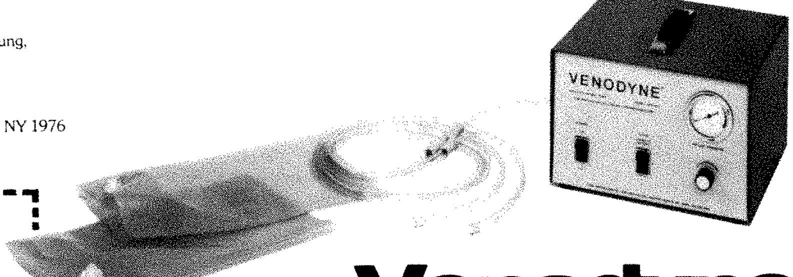
Early ambulation, leg exercises and elastic stockings have not significantly reduced the incidence of thrombophlebitic disease. Clotting normally commences before prophylactic measures have been instituted... usually while the patient is on the operating table. The various anticoagulants are the occasion of numerous contraindictions and complications.

Non-invasive, non-pharmacologic VENODYNE prophylaxis has been clinically shown to be as effective as anticoagulation, and much more effective than the various other physical methods of prophylaxis.

The VENODYNE system employs an inflatable plastic leg sleeve providing intermittent calf compression to simulate the normal calf muscle action of venous return. In essence, the system ambulates the patient on the operating table while under general anesthesia, or during any period of bed confinement. The system is safe, simple, and practical to use—and it's virtually trouble-free. Patient and nurse acceptance has been excellent.

Reprints of a number of professional papers on intermittent compression prophylaxis are available. **Write for free copies.**

1. *Cudkowicz and Sherry*, Heart and Lung, Vol 7, No 1, Jan-Feb 1978
2. *Gallus*, Venous Thromboembolism, Prevention and Treatment, Appleton-Century-Crofts, New York, NY 1976



Venodyne®
Exclusively from:
Lyne-Nicholson, Inc.
1000 Highland Ave., Needham Heights
MA 02194 Tel. 617-449-4900

Lyne-Nicholson, Inc.
1000 Highland Ave., Needham Heights
MA 02194 Tel. 617-449-4900

Reprints on intermittent compression prophylaxis

Name ______
Affiliation ______
Address ______
City ______ State ______ Zip ______
Telephone ______

Intraperitoneal Povidone-iodine in Experimental Peritonitis

M. CELESTE LAGARDE, M.D., JOHN S. BOLTON, M.D., ISIDORE COHN, JR., M.D.

From the Department of Surgery,
Louisiana State University School of Medicine,
New Orleans, Louisiana

Two experimental models were utilized to study the efficacy of intraperitoneal povidone-iodine in an established peritonitis. In both models, there was a 100% mortality in the povidone-iodine treated group. In laboratories which have reported favorable results, the animals were treated *before* peritonitis was allowed to develop. Clinical studies with povidone-iodine lavage have used dilute solutions which did not remain in the infected space. The effectiveness of this method was probably due to mechanical continuous irrigation. Our toxicity studies showed povidone-iodine to be fatal in normal animals in dosages exceeding 4.0 ml/kg. However, a dose of 2.0 ml/kg, which was nontoxic in normal animals, was fatal in animals with peritonitis. This study strongly suggests that the intraperitoneal administration of povidone-iodine can be fatal when the animal is compromised by peritonitis. The mechanism of this effect in unclear. On the basis of these studies, the intraperitoneal administration of povidone-iodine cannot be recommended for therapy of peritonitis.

IN ORDER TO REDUCE the considerable mortality associated with bacterial peritonitis, numerous agents have been administered intraperitoneally. Kanamycin and cephalothin have been shown to be effective both in this laboratory and others.[3,5-7,9,21,24] The success of these antibiotics depends on the bacteria present and their antibiotic sensitivity. Due to some toxic effects of antibiotics and the increasing problem with antibiotic-resistant bacterial strains, alternate agents have been studied for intraperitoneal instillation. Noxytiolin, a formaldehyde urea condensate, was ineffective in reducing peritonitis in experimental models.[10,16] Recently, povidone-iodine (Betadine solution®) has been used with some promising results for interparietal use,[12] prevention of wound infections,[11,27] peritoneal and mediastinal lavage,[14,29] and intraperitoneal instillation.[10,19]

Povidone-iodine is a water soluble complex of polyvinylpyrrolidone (PVP) and iodine. PVP is physiologically acceptable to animals and humans and has been used as a plasma expander. PVP has the ability to complex iodine, utilizing the antiseptic properties of iodine without the side effects of tissue irritation and staining. The PVP acts in a manner similar to plasma protein in combining with iodine with the result that iodine is converted to inorganic iodide at a much slower rate. The povidone-iodine (Betadine) used in these studies is an aqueous solution with 1.0% available iodine.[25,26]

The toxicity (LD_{50}), of this preparation following oral administration is 1300 mg free iodine/kg,[25] and is a function of available iodine. The toxic effects of iodine itself are largely due to its local action on the gastrointestinal tract when ingested orally. Little free iodine is absorbed from the gastrointestinal tract and the element enters the blood stream primarily in the form of iodide.[13]

The efficacy and safety of povidone-iodine solution in experimentally induced peritonitis were evaluated in order to answer questions concerning alternatives to intraperitoneal antibiotic administration. Increasing clinical application of this form of therapy also warranted critical documentation of its value.

Materials and Methods

Toxicity Studies

To determine a safe dose, toxicity studies were conducted in dogs and rats. Twenty-four mongrel dogs of either sex were anesthetized with 0.5 ml/kg of 3% sodium pentobarbital solution. The dogs were divided into five groups and were given 1.0 to 8.0 ml/kg of povidone-iodine solution by intraperitoneal injection.

Survival was determined at 24 hours. Twenty rats, anesthetized with diethyl ether, received povidone-iodine using the same dosage variation as in the dog. Survival was determined at 24 hours.

Experimental Peritonitis in the Dog Model

Forty-four adult mongrel dogs of either sex, weighing between eight and 32 kg were used. The animals were given no antibiotic prior to this procedure and were fasted the night before operation.

These dogs were anesthetized with 1.0 ml/kg of 3%

Presented at the Annual Meeting of the Southern Surgical Association, December 5-7 1977, Hot Springs, Virginia.

0003-4932-78-0600-0613-0085 © J. B. Lippincott Company

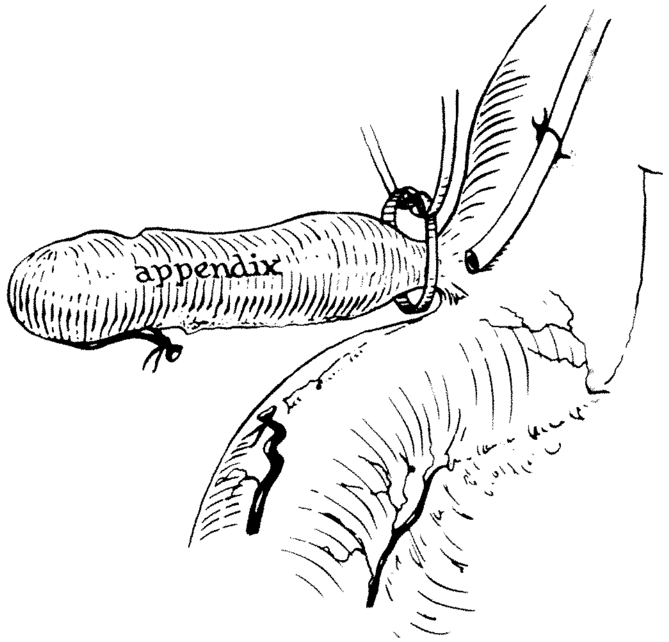


FIG. 1. Technique of appendiceal ligation. Plastic catheter is sutured to colon adjacent to appendix after ligation.

sodium pentobarbital, given intravenously. The method employed to produce peritonitis has been used previously in this laboratory (Figs. 1 and 2).[3,5–7] The cecum was identified and its blood supply and peritoneal attachments divided. The base of the cecum was ligated with umbilical tape. A 16 gauge, 20 cm flexible plastic catheter was then sutured to the colon adjacent to the appendiceal pouch. The abdomen was closed with 3-0 silk sutures and the catheter brought out through the midline. The skin was closed with 3-0 nylon. Postoperatively, the dogs were given 5 ml/kg of caster oil through an orogastric tube.

The animals were placed in three groups by random selection: one control and two treated. Twenty-four hours after ligation, blood and peritoneal fluid were obtained for culture (peritoneal fluid was obtained by aspiration from the catheter as was peritoneal fluid at the time of ligation). The control group received 100 ml saline via the intraperitoneal catheter. The kanamycin group received 500 mg kanamycin intraperitoneally in 98.5 ml saline to make a constant 100 ml volume. Povidone-iodine, 2.0 ml/kg diluted with saline to make a constant 100 ml volume, was injected intraperitoneally into the third group. The 2.0 ml/kg dose was established as safe in normal dogs. The animals were then observed until death, or until sacrifice after two weeks.

Experimental Peritonitis in the Rat Model

Experimental peritonitis in a rat model was treated with neutralized povidone-iodine solution to off-set any effect instillation of this acid solution (pH 2.43)[22] might have on the secondary metabolic acidosis of peritonitis. The neutralizing agent was $NaHCO_3$ since it is used clinically, and since it did not alter the physical appearance of the povidone-iodine. A solution of 4 ml $NaHCO_3$ plus 6 ml povidone-iodine measured pH 7.45.

A broth culture of *E. coli* (10^9/ml) suspended in 3.0% hemoglobin was injected intraperitoneally into 50 Charles River rats in a dose of 3.0 ml/kg after they were anesthetized with diethyl ether.[2,8,19,25] The rats were divided randomly into five groups. Two hours after inoculation, 30 of the rats were re-anesthetized and had injections as follows: 10 with 1.0 ml saline, 10 with 2.0 ml/kg povidone-iodine solution, and 10 with 2.0 ml/kg povidone-iodine solution neutralized with $NaHCO_3$.

Four hours after inoculation, the 20 remaining rats were reanesthetized and had injections as follows: ten with 2.0 ml/kg povidone-iodine, and ten with 2.0 ml/kg povidone-iodine neutralized with $NaHCO_3$. Survival was determined at 24 hours.

Total Serum Iodine Levels After Intraperitoneal Injection of Povidone-iodine in Dogs With and Without Peritonitis

Twenty dogs of either sex anesthetized with 1.0 ml/kg of 3% sodium pentobarbital solution were divided randomly into two groups (ten dogs each). Group 1 underwent laparotomy and suture of a flexible 20 cm, 16 gauge plastic catheter to the colon adjacent to the appendiceal pouch. Group 2 underwent the operation to produce peritonitis as previously described.

Twenty-four hours after operation, all dogs were given povidone-iodine, 2 ml/kg as an intraperitoneal injection via the plastic cannula. Blood samples were obtained at two, six, and 22 hours (or death) after the povidone-iodine injections. Total serum iodine levels

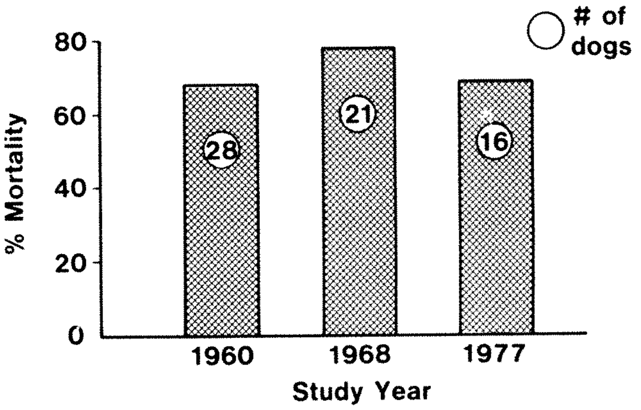


FIG. 2. Consistent mortality of untreated peritonitis in dogs over 17 year period, in various studies in our laboratories. The number of dogs in each experiment is encircled.

TABLE 1. *Toxicity of Intraperitoneal Providone-iodine in Dogs*

Ml/kg Povidone-iodine Solution Injected Intraperitoneally	Number of Dogs	Survival at 24 Hours
1.0	4	4/4
2.0	6	6/6
2.5	6	5/6
4.0	4	3/4
8.0	4	0/4

were determined after digestion of serum protein with concentrated sulfuric acid.[15]

Results

Toxicity Studies

Povidone-iodine solution was toxic in concentrations exceeding 4.0 ml/kg (Tables 1 and 2). The 2.0 ml/kg dose consistently showed no adverse effects when injected intraperitoneally into dogs and rats not challenged with peritonitis. Animals that died were autopsied. No gross organ abnormalities were noted. A moderate amount of peritoneal fluid was present. There was some brown staining but no free povidone-iodine remained in the peritoneal cavity.

Experimental Peritonitis in the Dog Model

None of the dogs treated with intraperitoneal povidone-iodine survived (Table 3). Eleven of the 12 dogs treated with kanamycin survived. Five of the 16 dogs that received saline survived. As reported previously,[7] kanamycin is effective in the treatment of advanced bacterial peritonitis ($p < .01$). There is also a statistically significant difference in survival rate between control and povidone-iodine treated groups ($p < .05$), indicating that povidone-iodine is not only ineffective but may be harmful when given by the intraperitoneal route in advanced peritonitis.

The dogs treated with intraperitoneal povidone-iodine had a markedly shortened survival time. Fifteen of these 16 dogs died within 24 hours after injection. One dog lived 48 hours. The average survival time of the dogs injected with saline was 96 hours.

TABLE 2. *Toxicity of Intraperitoneal Povidone-iodine Solution in Rats*

Ml/kg Povidone-iodine Solution Injected Intraperitoneally	Number of Rats	Survival at 24 Hours
1.0	4	4/4
2.0	4	4/4
2.5	4	4/4
4.0	4	2/4
8.0	4	0/4

TABLE 3. *Efficacy of Intraperitoneal Povidone-iodine Therapy in Peritonitis in Dogs*

Treatment	Total	Deaths	Death Rate
Control saline	16	11	69%
Kanamycin 500 mg	12	1	8%
Povidone-iodine 2.0 ml/kg	16	16	100%

The bacteriology of the peritoneal fluid 24 hours postligation showed no differences in the three groups. Clostridia were the predominant microorganisms, with *E. coli*, staphylococci, and streptococci following. Twenty per cent of the blood cultures were positive at 24 hours.

Animals that died from the experimental procedure within 48 hours postligation had a generalized peritonitis at autopsy. There was a moderate amount of foul-smelling purulent material. There were often bowel contents free in the abdominal cavity.

Survivors showed no evidence of peritonitis when autopsied. There were localized abscesses at the site of the ligated appendix. Adhesions involving the small bowel and omentum were also a consistent finding.

Experimental Peritonitis in the Rat Model

Because of the high mortality in the dog model, an alternative model was studied. Peritonitis was induced in rats by intraperitoneal injection of cultures of *E. coli*. The same dosages of $NaHCO_3$ neutralized povidone-iodine were used as in the dog model. There was, however, no significant difference in these results.

The control group had a 100% mortality (Table 4). The povidone-iodine solution was 100% fatal in this alternate experimental model. Only one animal survived in each neutralized group at two and four hours postinoculation. Groups 4 and 5 lived approximately

TABLE 4. *Efficacy of Intraperitoneal Povidone-iodine Therapy as Opposed to Neutralized Povidone-iodine in Peritonitis in Rats*

Group	Treatment by Intraperitoneal Injection	Untreated Interval After *E. coli* Injection	Number Survived 24 Hrs/ Total Number	Mean Survival in Hours
1	1.0 ml saline	2 hours	0/10	11.4
2	2.0 ml/kg povidone-iodine	2 hours	0/10	11.9
3	2.0 ml/kg povidone-iodine	4 hours	0/10	9.8
4	2.0 ml/kg povidone-iodine/ $NaHCO_3$	2 hours	1/10	12.9
5	2.0 ml/kg povidone-iodine/ $NaHCO_3$	4 hours	1/10	14.6

three hours longer. These results do not confirm a significant difference between povidone-iodine and its neutralized solution.

Total Serum Iodine Levels

Two of the dogs in Group 2 (peritonitis) died within 24 hours of appendiceal strangulation prior to povidone-iodine injection and were excluded from the study. The remaining eight dogs that received povidone-iodine after appendiceal strangulation died from two to 30 hours after injection. Autopsy in all cases revealed generalized peritonitis with from 200 to 600 ml of sanguinopurulent fluid in the peritoneal cavity. One of the ten dogs in Group 1 (laparotomy) died 100 hours after injection. At autopsy there was no obvious cause of death.

Iodine levels. Baseline total serum iodine levels were determined in three dogs, and were 5.3, 6.7, and 5.4 micrograms%. Total serum iodine levels after povidone-iodine injection are summarized in Table 5. Although both the peritonitis and laparotomy groups absorbed large amounts of iodine from the peritoneal cavity after injection of povidone-iodine, no significant differences were found between these two groups.

Discussion

Even though povidone-iodine has been studied extensively on the skin surface, little information is available regarding its intraperitoneal use. Interest was stirred when povidone-iodine was used as an intraperitoneal irrigant during the Vietnam conflict. But only Lavigne and Gilmore have reported intraperitoneal studies.

Lavigne[19] used a rat peritonitis model and reported toxicity results similar to ours. There was increased survival when povidone-iodine was injected one hour post-*E. coli* inoculation. But when the untreated interval was extended to two hours, mortality was 100%.

Gilmore[10] using a similar peritonitis model, had favorable results when the povidone-iodine preparation was injected immediately after *E. coli* inoculation. The povidone-iodine used, however, differed from Betadine solution in that it was a powdered form with only 0.1% available iodine. Also, povidone-iodine was used prophylactically since the peritoneal cavity was irrigated before peritonitis was allowed to develop. Our experimental models involved the therapeutic treatment of an established peritonitis, and the results are significantly different.

In some centers, povidone-iodine has been used clinically for peritoneal irrigation at approximately 50% dilution, with no documented harmful side effects.[23] Guignier[14] used a dialysis catheter to administer a dilute solution of povidone-iodine (Betadine), 10 ml in 1000 ml saline intraperitoneally at a rate of 500 ml/hour.

Thurer[29] treated patients with postoperative mediastinal infections with continuous povidone-iodine irrigation. A dilute solution, 50 ml povidone-iodine in 1000 ml saline was instilled through a catheter at a rate of 50–100 ml/hour. Ochsner[20] reported irrigation of an infected chest cavity with full strength povidone-iodine solution. The patient developed symptoms of iodine toxicity, and a more dilute solution was used.

The mechanical effect of continuous irrigation is an important part of the efficacy of povidone-iodine lavage. The activity of the povidone-iodine complex is diminished in the presence of blood or serum. Necrotic wounds and purulent burn wounds harboring bacteria require repeated applications to allow the iodine to come in direct contact with the infection.[4]

Our data indicate that povidone-iodine is ineffective when given intraperitoneally in the treatment of the model of peritonitis we used, and that it may even

TABLE 5. *Total Serum Iodine Levels After Povidone-iodine Intraperitoneal Injection (Dogs)*

Group 1 Laparotomy Total Serum Iodine (Micrograms %)				Group 2 Appendiceal Strangulation Total Serum Iodine (Micrograms %)				
Dog	2 hrs	6 hrs	22 hrs	Dog	2 hrs	6 hrs	22 hrs	Death
1	380	1700	9600	1	940	—	—	—
2	860	3200	14000	2	410	1200	8000	—
3	740	2400	12200	3	600	2300	—	—
4	520	1950	6200	4	550	3200	—	13800 (20 hrs)
5	1100	5400	17000	5	340	1900	—	—
6	680	2400	9600	6	540	1050	—	—
7	730	1520	9100	7	780	2200	—	10000 (14 hrs)
8	1100	3500	10500	8	700	3800	—	16500 (13 hrs)
9*	390	1600	9600					
10	480	2300	10400					
Mean	697	2597	10820	Mean	610	2235	8000	13430

* This control animal died 100 hrs after povidone-iodine injection.

contribute to mortality when used in advanced peritonitis. One possible explanation of the increased mortality might be the development of metabolic acidosis after the use of povidone-iodine. This has been described by Lavelle[17] and Pietsch,[22] who demonstrated systemic absorption of large amounts of iodine from extensively burned patients treated with topical povidone-iodine ointment. Four of these patients died after developing an unexplained, severe metabolic acidosis early in their hospital course.

Our attempts to neutralize the aqueous solution of povidone-iodine by addition of $NaHCO_3$ prior to intraperitoneal injection did not increase survival significantly in rats with peritonitis. However, the *in vitro* reduction of iodine to iodide by $NaHCO_3$ might destroy its germicidal activity. Lavelle[19] described hepato- and nephrotoxicity in burn patients treated with povidone-iodine topical ointment, but Blanco and Rothwell[1] found no evidence of serial changes in BUN and serum creatinine in a retrospective review of selected burn patients treated with povidone-iodine topical ointment and concluded that iodine-caused nephrotoxicity did not occur in this setting.

Some deleterious effects have been attributed to the iodides as well. Lavelle[17,18] produced histological and chemical evidence of kidney and liver damage after infusion of sterile, buffered NaI in rabbits in doses sufficient to raise total serum iodine levels from 48.4 to 186 mgm% and also produced acidosis in rabbits by infusing sterile, buffered sodium iodide solution. Others[30,31] have noted dyspnea, acute pulmonary edema, pleural effusions, and kidney and liver toxicity.

In our study, the increase mortality in povidone-iodine treated groups might be due to the development of systemic iodine toxicity following transperitoneal absorption of iodine. We have documented the absorption of large quantities of iodine after intraperitoneal injection of povidone-iodine in dogs as had been reported earlier by Lavigne in rats.[19]

The amounts of iodine in the povidone-iodine solution used in this study are considerably lower than the amount of sodium iodide reported by other investigators to produce systemic iodism. However, the total serum iodine levels in several of our animals (both laparotomy and peritonitis groups, (Table 5) approached the levels measured in the burn patients reported by Lavelle[17] and Pietsch.[22] The fact that the total serum iodine levels were equally elevated in laparotomy and peritonitis groups argues against iodine toxicity alone as the cause of the increased mortality in the povidone-iodine treated peritonitis dogs in this experiment. The possibility that systemic iodine toxicity might develop with lower serum iodide loads in the face of peritonitis cannot be excluded.

An alteration of the peritoneal response to infection in the presence of povidone-iodine may also explain the increased mortality in peritonitis treated with povidone-iodine. Free hemoglobin decreases the peritoneal clearance of microorganisms,[2,28] allowing a more rapid intraperitoneal increase of bacteria. This results in an increased production of bacterial endotoxins, their absorption, and the production of endotoxic shock. Since povidone has been used as a plasma expander and resembles the porphyrin ring of hemoglobin in some respects,[25] its intraperitoneal use in bacterial peritonitis might be deleterious, particularly if the bactericidal moiety, iodine, is quickly inactivated by *in vivo* reduction to iodide. The presence of other possible lethality-enhancing substances, such as surfactants, in commercially available aqueous solutions of povidone-iodine cannot be excluded.

Even with all these possible explanations taken into account some important features of this work stand out, the most prominent of which is the observation that in one or more standard models of peritonitis, the addition of povidone-iodine to the peritoneal cavity enhances the lethality of peritonitis. Studies in control dogs and rats have demonstrated safe as well as lethal doses of intraperitoneally administered povidone-iodine. In a rat model of peritonitis which does not involve any surgical procedure, but depends on the intraperitoneal injection of a standard quantity of a known culture of a standard organism, povidone-iodine did not lower the mortality from control levels, and the neutralization of the povidone-iodine did little to alter this high mortality rate. In the appendicitis-peritonitis model in the dog, an experimental model with which this laboratory has over 17 years of consistent experience (Fig. 2), the addition of povidone-iodine to the peritoneal cavity significantly increased mortality over both control and kanamycin treated animals. In these animals no difference could be detected between serum iodine levels in control and treated animals, and therefore it seems unlikely that the systemic absorption of iodine alone could have accounted for the great increase in mortality. Without being able to explain all the changes that have taken place, it seems safe to conclude from these studies that intraperitoneal administration of povidone-iodine in the animal subjected to peritonitis is unwise. Clinical use of intraperitoneal povidone-iodine cannot be recommended in the face of these results.

References

1. Blanco, C. and Rothwell, K. G.: Povidone-iodine and the Kidney. Lancet, 1:911, 1976.
2. Bornside, G. H., Bouis, P. J., Jr. and Cohn, I., Jr.: Hemoglobin and *Escherichia coli*, a Lethal Intraperitoneal Combination. J. Bacteriol., 95:1567, 1968.

3. Cohn, I., Jr. and Cotlar, A. M.: Intraperitoneal Kanamycin. Ann. Surg., 155:533, 1962.
4. Connell, J. F., Jr. and Rousselot, L. M.: Povidone-iodine. Extensive Surgical Evaluation of a New Antiseptic Agent. Am. J. Surg., 108:849, 1964.
5. Cotlar, A. M., Massari, F. S. and Cohn, I., Jr.: Intraperitoneal Kanamycin in the Treatment of Peritonitis. Antimicrob. Agents Annual 1960, New York, Plenum, 1961, pp. 386–391.
6. Crook, J. N., Cotlar, A. M., Bornside, G. H. and Cohn, I., Jr.: Intraperitoneal Cephalothin in the Treatment of Experimental Appendiceal Peritonitis. Am. Surg., 34:736, 1968.
7. DiVincenti, F. C. and Cohn, I., Jr.: Intraperitoneal Kanamycin in Advanced Peritonitis. Am. J. Surg., 111:147, 1966.
8. Filler, R. M. and Sleeman, H. K.: Pathogenesis of Peritonitis. I. The Effect of *Escherichia coli* and Hemoglobin on Peritoneal Absorption. Surgery, 61:385, 1967.
9. Fowler, R.: A Controlled Trial of Intraperitoneal Cephaloridine Administration in Peritonitis. J. Pediatr. Surg., 10:43, 1975.
10. Gilmore, O. J. A.: A Reappraisal of the Use of Antiseptics in Surgical Practice. Ann. R. Coll. Surg. Engl., 59:93, 1977.
11. Gilmore, O. J. A., Martin, T. D. M. and Fletcher, B. N.: Prevention of Wound Infection after Appendicectomy. Lancet, 1:220, 1973.
12. Gilmore, O. J. A. and Sanderson, P. J.: Prophylactic Interparietal Povidone-iodine in Abdominal Surgery. Br. J. Surg., 62:792, 1975.
13. Goodman, C. and Gilman, A.: The Pharmacological Basis of Therapeutics. New York, Macmillan, 1975, pp. 995–996.
14. Guignier, M., Brambilla, C., Brabant, A., et al.: Les Lavages Peritoneaux a la Polyvinylpyrrolidone Iodee. A Propos de 11 Cas. Nouvelle Presse Medicale, 3:1559, 1974.
15. Henry, R. J.: Clinical Chemistry: Principle and Technics. New York, Harper and Row, 1964, pp. 925–950.
16. King, D. W., Curry, J. F. and Brooke, B. N.: The Effect of Noxytiolin in Experimental Peritonitis. Br. J. Surg., 62:645, 1975.
17. Lavelle, K. J., Doedens, D. J., Kleit, S. A. and Forney, R. B.: Iodine Absorption in Burn Patients Treated Topically with Povidone-iodine. Clin. Pharmacol. Therapeut., 17:355, 1975.
18. Lavelle, K. J., Doedens, D. J., Kleit, S. A. and Forney, R. B.: Toxicity of Sodium Iodide in the Rabbit: Effects of Hydrogen Ion Homeostasis, Hepatic and Renal Functions. Toxicol. Appl. Pharmacol., 33:52, 1976.
19. Lavigne, J. E., Brown, C. S., Machiedo, G. W., et al.: The Treatment of Experimental Peritonitis with Intraperitoneal Betadine Solution. J. Surg. Res., 16:307, 1974.
20. Lord, J. W., Jr., Rossi, G. and Daliana, M.: Intraoperative Antibiotic Wound Lavage. Ann. Surg., 185:634, 1977.
21. McMullan, M. H. and Barnett, W. O.: The Clinical Use of Intraperitoneal Cephalothin. Surgery, 67:432, 1970.
22. Pietsch, J. and Meakins, J. L.: Complications of Povidone-iodine Absorption in Topically Treated Burn Patients. Lancet, 1: 280, 1976.
23. Polk, H.: Personal Communication, 1977.
24. Rambo, W. M.: Irrigation of the Peritoneal Cavity with Cephalothin, Am. J. Surg., 123:192, 1972.
25. Shelanski, H. A. and Shelanski, M. V.: PVP-iodine: History, Toxicity and Therapeutic Uses. J. Int. Coll. Surg., 25:727, 1956.
26. Siggia, S.: The Chemistry of Polyvinylpyrrolidone-iodine. J. Am. Pharm. Assoc., 46:201, 1957.
27. Sindelar, W. F. and Mason, G. R.: Efficacy of Povidone-iodine Irrigation in Prevention of Surgical Wound Infections. Surg. Forum, 28:48, 1977.
28. Sleeman, H. K., Diggs, J. W., Hendry, W. S. and Filler, R. M.: Pathogenesis of Peritonitis II: The Effect of *Escherichia coli* and Adjuvant Substances on Peritoneal Absorption. Surgery, 61:393, 1967.
29. Thurer, R. J., Bognolo, D., Vargas, A., et al.: The Management of mediastinal Infection Following Cardiac Surgery. An Experience Utilizing Continuous Irrigation with Povidone-iodine. J. Thorac. Cardiovasc. Surg., 68:962, 1974.
30. Trotter, W. R.: A Comparison of the Acute Toxic Effects of Iodides and Thiourea Derivatives. Br. J. Exp. Pathol., 33: 202, 1952.
31. Webster, S. H., Rice, M. E., Highman, B. and Von Oettingen, W. F.: The Toxicology of Potassium and Sodium Iodates: Acute Toxicity in Mice. J. Pharmacol. Exp. Therapeut., 120: 171, 1957.

DISCUSSION

DR. ROBERT ZEPPA (Miami, Florida): I'd like to point out that there is no question that under the conditions of this experiment the data are clear, and I think the conclusions are clear as well. Their relationship, however, to the clinical situation requires, I think, some interpretation.

In the first place, the infections which were constituted in these animals were invasive infections, and the authors attempted to treat invasive infection with a single dose of a topical antiseptic agent, which I don't think one would expect to have salubrious effects upon longevity. Kanamycin, of course, was absorbed, and is a systemic antibiotic, and obviously modified the course of these animals.

The way we use this agent, at least in most of the clinical situations with which I am familiar, has been to use it as an irrigant. And here one would really need to know whether there's any advantage to utilizing a dilute solution of the povidone-iodine material as an irrigant in the same volume as saline, or anything else, as an adjuvant to the therapy of an invasive infection such as peritonitis.

I say "invasive infection" because in the manuscript Dr. Cohn very carefully points out that he does have positive blood cultures in these animals.

Secondly, the data that had accumulated prior to the establishment of this material as an effective agent for cleansing of the skin suggested that a two minute contact was all that was necessary to provide topical antisepsis. And in some experiments conducted in our institution by Drs. Lestor, Arango, and Malinin, which are different than these and may have no direct bearing on these results—however, they did show in attempting to standardize irrigation techniques, there seemed to be an advantage to using povidone-iodine.

Furthermore, the culture studies in this study would suggest that the povidone-iodine has no effect at all upon the bacteria. (Slide) This is a technique for sterilization of the bowel. I'm sure that those of you who are familiar with the work of DeCosse, and others—this has been going on simultaneously in our institution, unbeknownst to us that it was being done elsewhere.

(Slide) The next slide shows in humans, now—these are trauma patients—the bacteriological studies on the contents of treated and untreated colon segments in 25 patients. Whether it was the proximal segment or the distal segment, cultures became negative in these segments in a very, very high percentage after treatment with povidone-iodine.

I would also like to suggest that one of the features of povidone-iodine which may lead to increased toxicity in dogs, at any rate, is the polyvinylpyrrolidone. When this material was being studied for use as a plasma expander, it was discovered that dogs were highly susceptible to it. They developed renal failure, and also hypotension. This particular polymer is a very potent disrupter of the dog mast cell system, which aggravates the shock, if it does nothing else.

The absorption of polyvinylpyrrolidone could have been enhanced by virtue of the inflammation of the peritoneal cavity.

Dr. Lewis Flint (Louisville, Kentucky): Using a cecal ligation preparation, Dr. Cohn and his coworkers have observed a 68% mortality for saline-treated dogs, a 100% mortality for Betadine-treated dogs, and an 8% mortality for dogs treated with intraperitoneal kanamycin. They have concluded that Betadine is ineffective, and possibly harmful.

These findings contrast with our clinical impressions in nearly 100 patients now, using a dilute solution of Betadine peritoneal lavage, intraoperatively, that approximates a dose of about 2 cc/kg.

There are, to my mind, four issues which may alter the conclusion.

First, the mortality of the untreated model has remained constant at LSU since 1960. The mortality for the Betadine treated dogs is remarkably high, but is no more striking than the 8% mortality for the kanamycin-treated group, which is remarkably less than the 28% mortality for similarly treated dogs reported by Cohn and Cotlar.

Does this indicate a possible error in the design of the experiment?

This experimental preparation has been difficult for me to master, and so I am cautious concerning small details, such as the sex distribution of animals within groups. A study conducted by Drs. Fry, Richardson, and myself showed that the 30 hour mortality for penicillin-treated dogs with cecal ligation was 22% for males and 90% for females.

As to the conclusions, the efficacy of kanamycin is clear. However, the drug has the advantage of continued action following absorption. Following the absorption of the iodine, it is inactive. Finally, several studies have shown rapid equilibration of antibiotics into peritoneal fluid, leading to uniform distribution of kanamycin at the site of the infection. Was Betadine similarly distributed? If not, the groups are not comparable.

Any antimicrobial agent instilled into the peritoneal cavity should have the appropriate antibacterial spectrum, be nontoxic, and have low systemic absorption. The search for the ideal agent should continue.

Dr. G. Robert Mason (Baltimore, Maryland): The attention here today has been primarily oriented at the peritoneum. We have learned, I think, over many years, that the peritoneum is pretty well able to take care of itself, and Dr. Stone showed us that the more we do to it, the worse off we are.

I would like to direct your attention a little to the wound itself. We have recently continued, and have completed, a study at the University of Maryland of approximately 500 patients in which the wound has been irrigated, randomized, with saline and Betadine. These incisions have been divided into those which were clean, potentially contaminated, and truly contaminated.

In this study we have found definitely that there is a reduction in the wound infection when povidone-iodine is used.

Now, this started out this afternoon as a pediatric afternoon. I'd like to direct our attention to what I think is our baby. I think our baby really is the wound infection. And I would urge you not to throw out the baby with iodinated bath water. Thank you.

Microsurgical Composite Tissue Transplantation

DONALD SERAFIN, M.D., NICHOLAS G. GEORGIADE, M.D.

From the Division of Plastic and Reconstructive Surgery,
Duke University Medical Center,
Durham, North Carolina

Since 1974, 69 patients with extensive defects have undergone reconstruction by microsurgical composite tissue transplantation. Using this method, donor composite tissue is isolated on its blood supply, removed to a distant recipient site, and the continuity of blood flow re-established by microvascular anastomoses. In this series, 56 patients (81%) were completely successful. There have been eight (12%) failures, primarily in the extremities. There have been five (7%) partial successes, (*i.e.*, a microvascular flap in which a portion was lost requiring a secondary procedure such as a split thickness graft). In those patients with a severely injured lower extremity, the failure rate was the greatest. Most of these were arterial (six of seven). These failures occurred early in the series and were thought to be related to a severely damaged recipient vasculature. This problem has been circumvented by an autogenous interpositional vein graft, permitting more mobility of flap placement. In the upper extremity, all but one case were successful. Early motion was permitted, preventing joint capsular contractures and loss of function. Twenty-three cases in the head and neck region were successful (one partial success). This included two composite rib grafts to the mandible. Prolonged delays in reconstruction following extirpation of a malignancy were avoided. A rapid return to society following complete reconstruction was ensured. Nine patients presented for reconstruction of the breast and thorax following radical mastectomy. All were successfully reconstructed with this new technique except one patient. Its many advantages include immediate reconstruction without delayed procedures and no secondary deformity of the donor site. Healthy, well vascularized tissue can now be transferred to a previously irradiated area with no tissue loss. This new method offers many advantages to older methods of reconstruction. Length of hospital stay and immobilization are reduced. The total number of operative procedures required in achieving the desired result is also less, thus decreasing the cost of hospital care.

MICROSURGICAL COMPOSITE TISSUE transplantation entails the complete detachment of large segments of tissue of varied histological types with subsequent transfer and immediate revascularization at a distant recipient site. Both detachment and revascularization are completed during a single, relatively short operative procedure. Lengthy tissue delays with prolonged immobilization by cumbersome pedicle attachment are eliminated.

Using this new method of reconstruction, composite tissue can be successfully transferred to reconstruct extensive recipient defects, with minimal deformity of the donor site. Skin and subcutaneous tissue can be transferred to cover bone denuded of periosteum, with nerves or tendons exposed.[20] Segments of missing bone can be replaced and immediately revascularized with resulting rapid healing and callus formation.[16,23] Skeletal muscle can be successfully transplanted with eventual return of voluntary contraction and restoration of function.[6,8,26]

Immediate revascularization is achieved by the microsurgical anastomosis of the donor vasculature to that of the recipient site. The selection with successful transfer of suitable donor tissue is predicted on the location of a single vascular pedicle containing a nutrient artery and communicating drainage veins.

History

Early and continuing efforts in replantation have contributed considerably to the development of the rapidly growing subspecialty of microsurgery.[4,7,10,11,13] Research in the experimental laboratory has also provided an understanding of factors influencing anastomotic patency and blood flow in the microcirculation.[1-3,12,24,25] Blood vessels with external diameters measuring 0.8–1.0 ml, whose continuity has been completely interrupted, can now have blood flow restored with predictable patency rates.[9]

Following the first successful description of the clinical transplantation of omentum to a large scalp defect by McLean and Buncke in 1972,[14] the literature has become replete with similar reports.[5,15,22]

Major medical centers and residency training programs throughout the world now feel that experience

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Reprint requests: Donald Serafin, M.D., Division of Plastic and Reconstructive Surgery, Duke University Medical Center, Durham, North Carolina, 27710.

0003-4932-78-0600-0620-0105 © J. B. Lippincott Company

in microsurgery should be an integral part of their curriculum.

Clinical Series

Since 1974, 69 patients with extensive bone and soft tissue defects have undergone reconstruction by microsurgical composite tissue transplantation. Considerable thought was given to the selection of these patients for this type of reconstruction. Problems easily solved by older existing methods were excluded from consideration. In this series of patients (Table 1), reconstruction by this new method was successful in 56 patients (81%), partially successful in five (7%), and unsuccessful in eight (12%). A flap was felt to be partially successful if, in spite of a partial loss, it was able to fulfill its intended function with only a limited additional surgical procedure such as a skin graft. The results in this present series compare most favorably to older, existing methods of reconstruction, especially when several different parameters which determine a successful result are also examined.

Different types of composite tissue were employed in the reconstruction of four anatomic regions, each presenting unique characteristics which influenced the success of the final result (Table 2). The vascularized groin flap was most frequently employed, but myocutaneous and osteocutaneous composite tissue was also successfully transferred. (The latissimus dorsi myocutaneous (subscapular) flap is being used with increased frequency because of the constancy of its blood supply and minimal deformity of the donor site).

Head and Neck

Reconstruction in the head and neck region was carried out in 23 patients. Almost all were completely successful. In this region, extensive defects resulted from trauma in 12 patients and in 11 patients following extirpation of a malignancy.[19] Most of the cases resulting from trauma were reconstructed later, whereas those resulting from malignancy were reconstructed early, often during the same hospitalization. Two patients underwent both the extirpative and reconstructive portion of the procedure during a single operative procedure (Figs. 1a–d).

Early reconstruction with healthy, well-vascularized composite tissue permits the rapid return to society of a patient, with minimal physical and psychological mutilation. A rapid return to gainful employment is encouraged. This minimizes the total economic loss to the patient and enhances his self-image. If adjunctive radiotherapy or chemotherapy is indicated, this can be instituted at a much earlier date, perhaps enhancing survival statistics.

The high success rate in this region reflects the quality and availability of suitable vasculature. An interpositional vein graft is seldom required. Previous radical neck dissection or radiation, however, may

TABLE 1. *Microvascular Flaps—Regional Distribution*

Number	Area
23	Head and neck
11	Breast and thorax
8	Upper extremity
27	Lower extremity

TABLE 2. *Microvascular Flaps—Composite Tissue Type*

Number	Type
56	Groin flaps
3	Subscapular flaps
1	Dorsalis pedis flap
2	Osteocutaneous flaps
6	Rib periosteal flaps
1	Gracilis myocutaneous flap

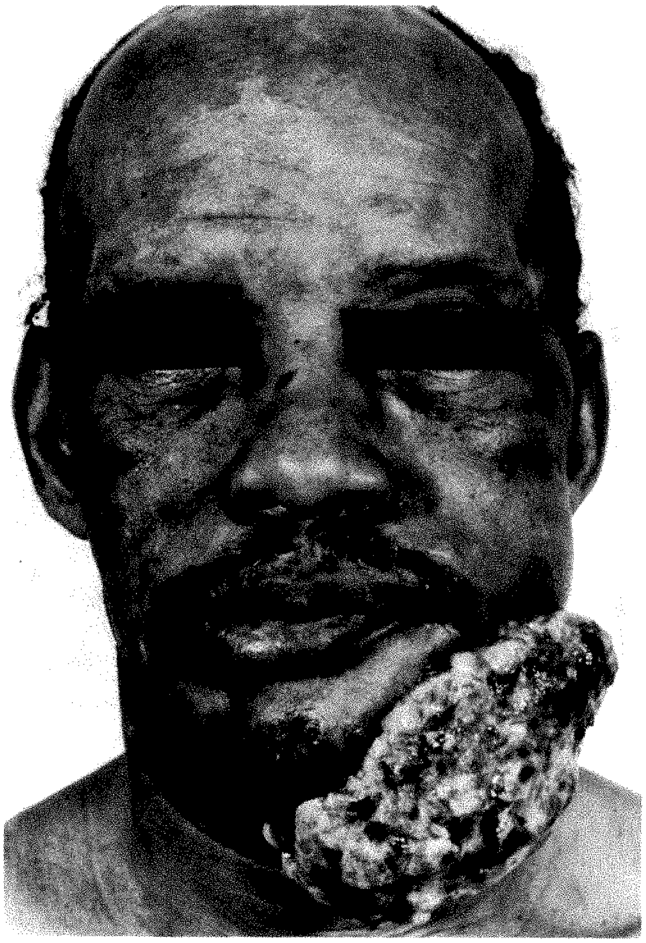


FIG. 1a. Preoperative photograph demonstrating Stage III Squamous Carcinoma left alveolar ridge.

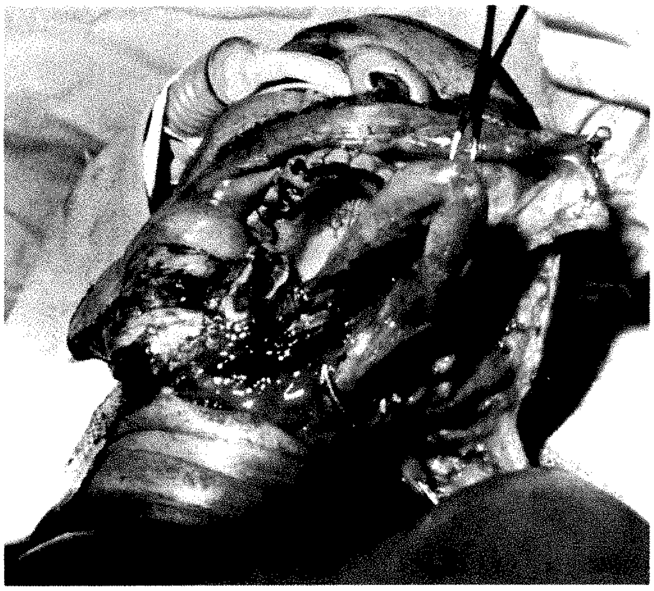


FIG. 1b. Intraoperative photograph demonstrating composite resection with extensive loss of mucosa, bone and overlying skin.

increase the difficulty of reconstruction and vascular anastomosis. Detailed preoperative planning is mandatory.

Breast and Thorax

Nine patients have undergone breast reconstruction following mastectomy with vascularized groin flaps (Figs. 2a–e). Four patients in this group received postoperative radiation and one, postoperative chemotherapy. Four patients had such extensive radical mastectomies that a split thickness skin graft was required to achieve primary wound closure. In eight patients, reconstruction was completely successful, whereas in one, reconstruction was complicated by flap necrosis necessitating a skin graft.

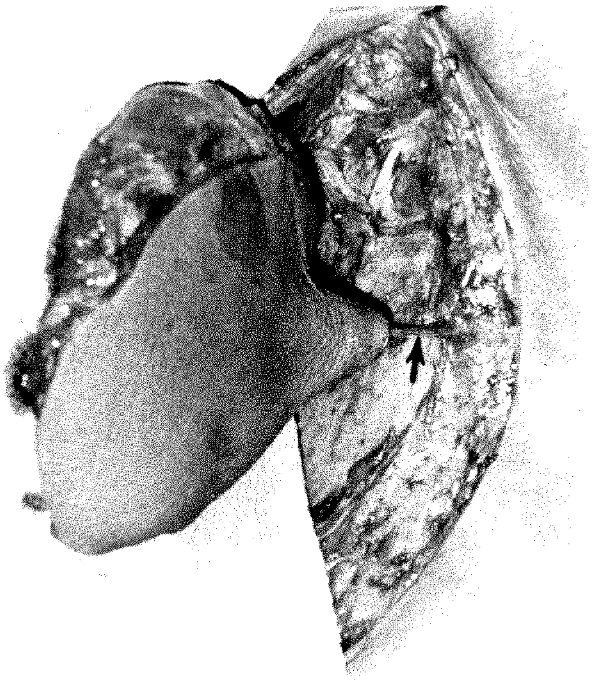


FIG. 1c. Intraoperative photograph of subscapular flap isolated on vascular pedicle (arrow) prior to transplantation.

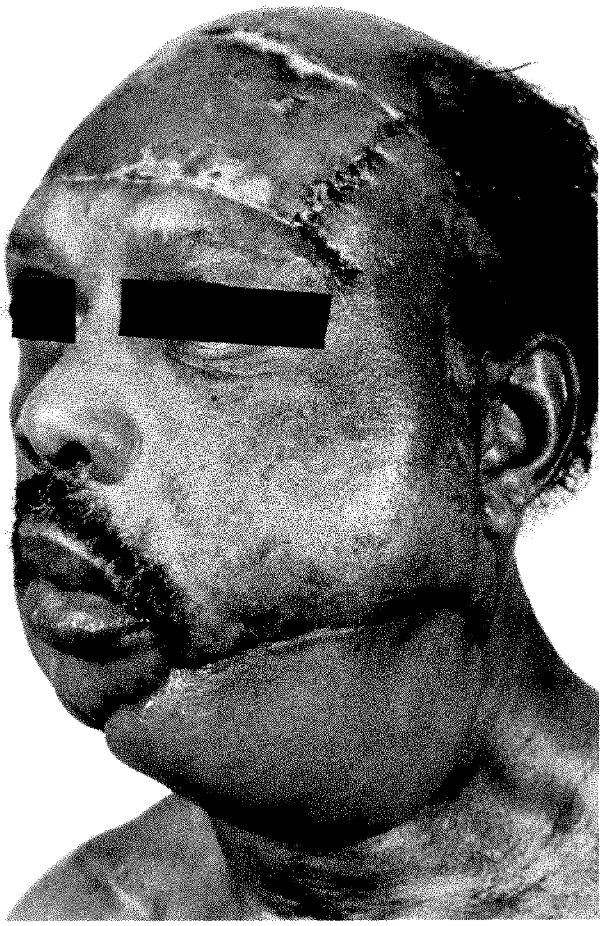


FIG 1d. Postoperative result. Note forehead flap used for intraoral reconstruction in conjunction with subscapular flap.

Reconstruction was usually complete within one year, consisting of three separate stages. In the first stage, radiation damaged skin or a previously placed skin graft was removed and replaced with a healthy well-vascularized composite flap. An interpositional vein graft was frequently required to provide good arterial blood flow from the axillary artery to the donor artery of the flap.

During the second stage, three months later, the vascularized flap was augmented with a silastic gel prosthesis and a subcutaneous mastectomy performed on the contralateral breast. Breast mound symmetry was achieved at this time.

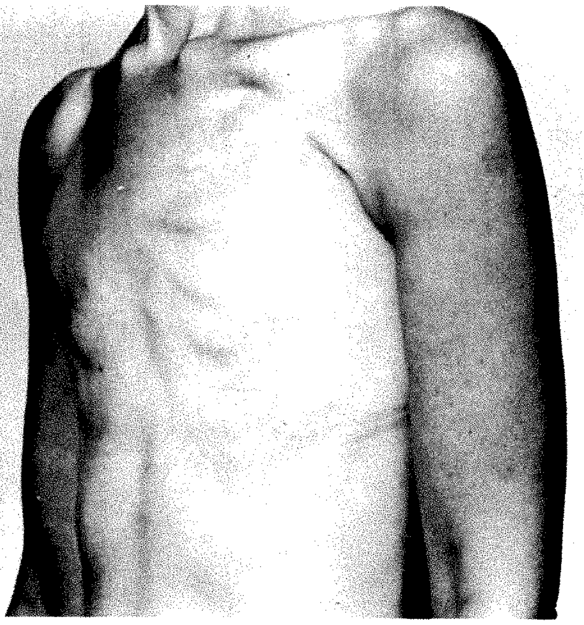


FIG. 2a. Preoperative photograph demonstrating a patient with left radical mastectomy and right modified mastectomy for invasive lobular carcinoma.

Finally, during the third the final stage, a nipple–areolar complex is reconstructed two to three months later.

Thorax reconstruction was conducted successfully in two patients who developed local chest wall recurrence of a malignancy (Figs. 3a–d). An en bloc dissection consisting of soft tissue and associated underlying three ribs was performed, as well as immediate wound closure with a vascularized composite flap.

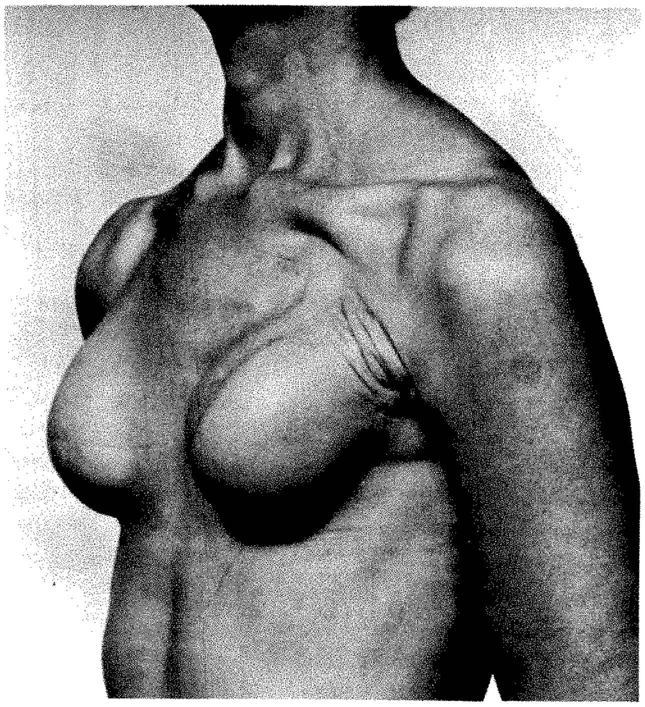


FIG. 2b. Postoperative photograph demonstrating vascularized groin flap to reconstruct left breast and bilateral augmentation to create breast mound symmetry.

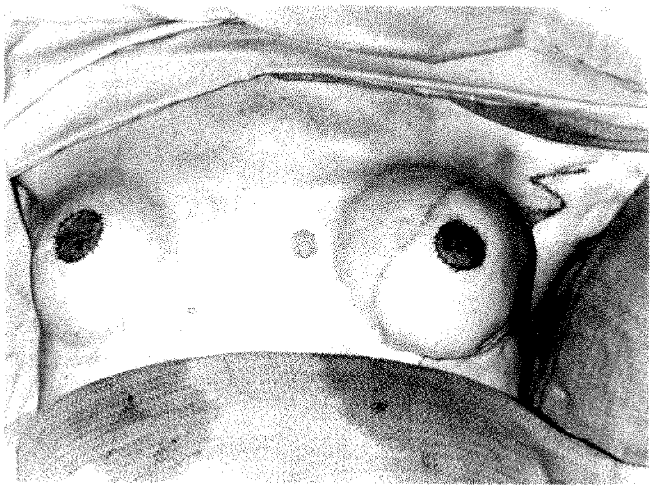


FIG. 2c. Intraoperative photograph demonstrating nipple—areolar reconstruction with labial grafts.

Upper Extremity

Reconstruction of the upper extremity was performed in eight patients. In this group six were successful, one partially successful, and one failed. In most instances full thickness, healthy, well-vascularized skin was required prior to bone fusion, tendon transfer

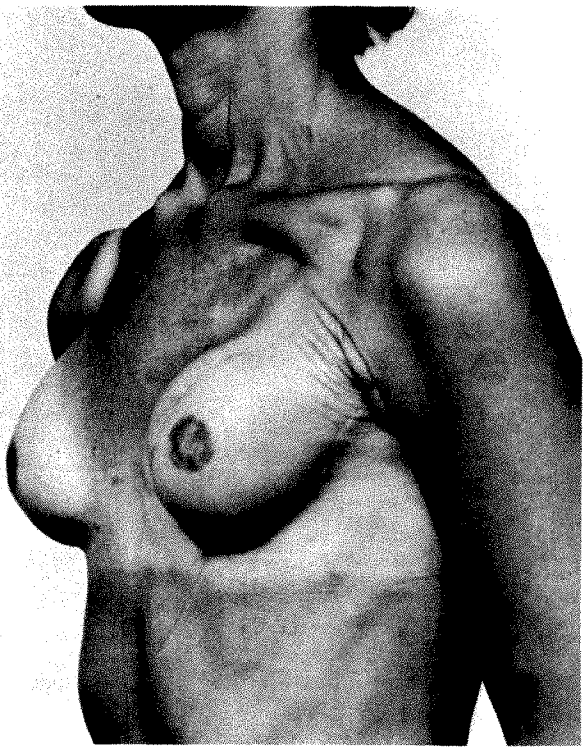


FIG. 2d. Late postoperative result.

FIG. 3a. Preoperative photograph demonstrating chest wall recurrence carcinoma breast, ten years following mastectomy. Note radiation changes.

or nerve grafting. Almost all patients had extensive defects resulting from previous trauma.

In one patient, skin and flexor muscle loss was so extensive that a vascularized compound gracilis myocutaneous flap was required for reconstruction (Figs. 4a–e). Median nerve continuity was restored by a sural nerve fasicular graft. Reinnervation of the gracilis muscle was accomplished by a fasicular nerve anastomosis between a branch of the obturator nerve of the muscle and the anterior interosseous nerve.

Lower Extremity

Reconstruction of the lower extremity with vascularized composite tissue was performed in 27 patients (Figs. 5a–c). In this group 18 were completely successful, three partially successful and six failed. The failure rate in this group was the highest, reflecting the considerable difficulties encounted early in our experience dealing with the extensively damaged recipient vasculature. More recently this problem has been circumvented by the frequent use of the interpositional vein graft to restore arterial flow. A damaged segment of recipient artery can thus be bypassed without the restriction of flap placement or interruption of arterial continuity.

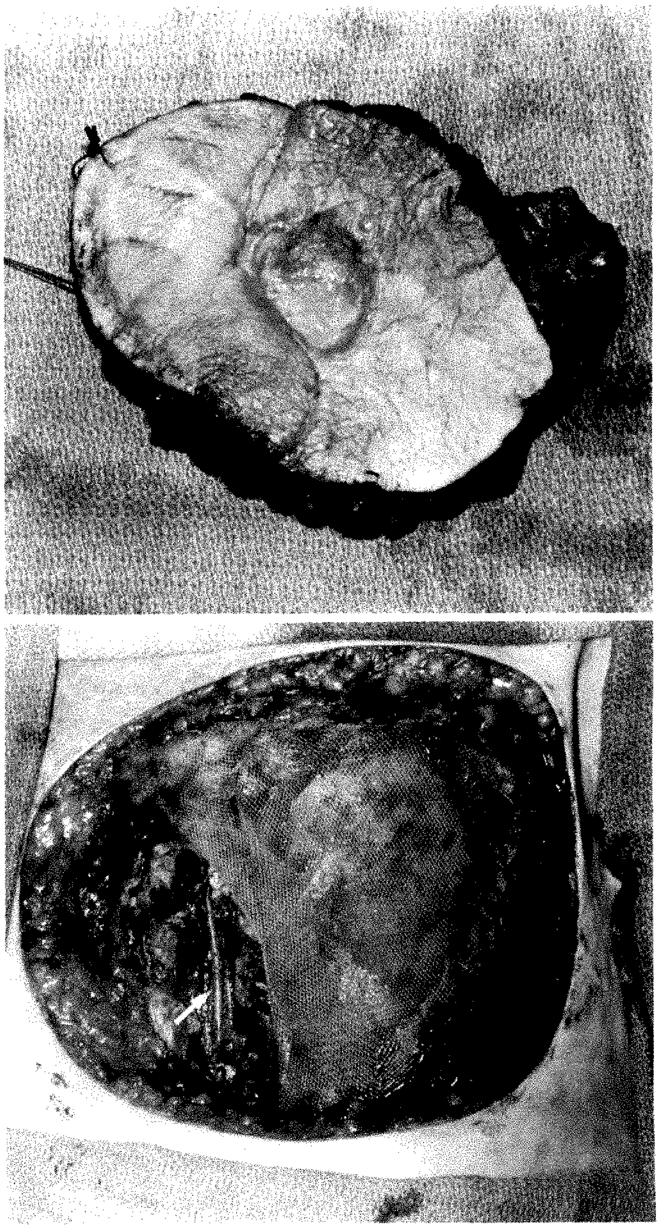
Careful comparison of this new method of lower extremity reconstruction to older, existing methods revealed that it is superior.[20] Flap survival statistics compare favorably to these older methods. Patient and flap morbidity have been significantly reduced, which is a reflection of the superiority of this method and the minimal period of immobilization and hospitalization.

Discussion

The failure rate of 12% in the present series, although significant, compares favorably with other, existing methods of reconstruction. These flap survival statistics reflect our total experience, especially those failures early in the series.

A careful review of the present series also revealed that 29% (20 patients) had evidence of vascular insufficiency, 19% (13 patients) requiring exploration of the anastomotic site.[21] A successful result was achieved in six patients. Although the incidence of arterial and venous insufficiency was approximately equal, most of the complete and partial failures were arterial.

A detailed review of these arterial failures suggests that they were the result, in many instances, of the



FIGS. 3b and c. (b, top) Intraoperative photograph demonstrating resected specimen. (c, bottom) Intraoperative photograph demonstrating with merselene mesh to stabilize chest wall. Note recipient internal mammary artery and vein (arrow).

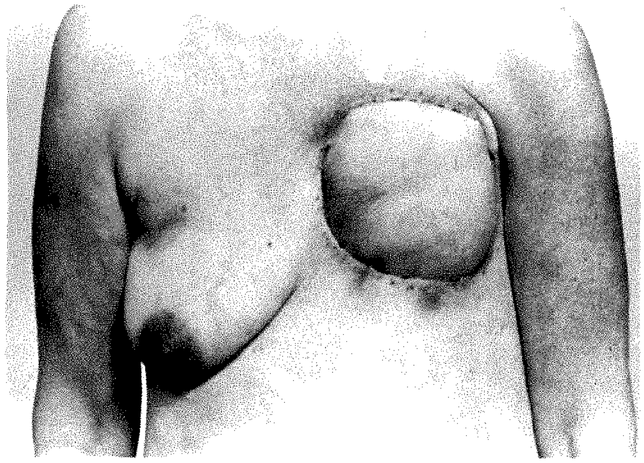


FIG. 3d. Late postoperative result.

damaged recipient vascular bed. This problem has been corrected, in part, by precise preoperative and intraoperative planning with emphasis on the selection of suitable, undamaged vasculature. Preoperative arteriograms, especially in extremity reconstruction, are essential.

The reversed interpositional vein graft has significantly improved flap survival statistics by ensuring adequate arterial flow.[17] Composite tissue placement is no longer restricted to the damaged recipient vasculature. Also, by using this technique and employing an end-to-side anastomosis from the interpositional vein graft to the recipient artery, continuity of the recipient artery is not interrupted. This is especially important when the number of major uninjured arteries to an extremity is limited.

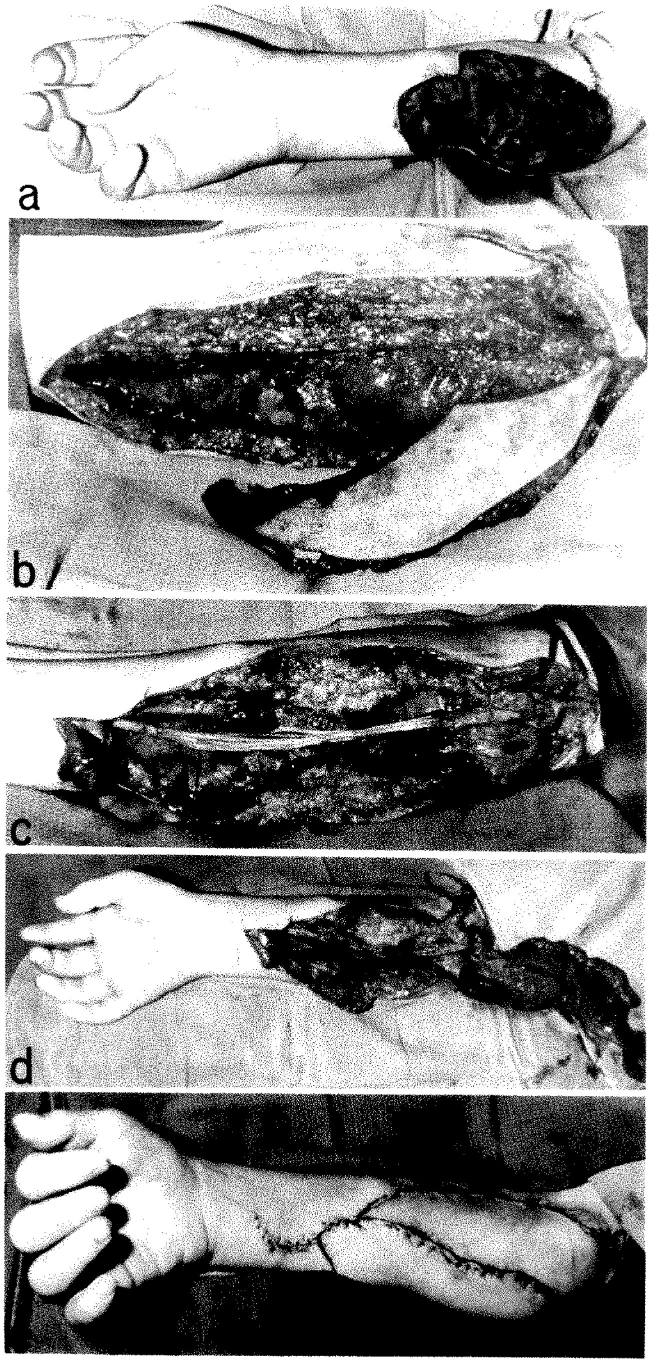
The location of suitable recipient veins, in general, is less of a problem. With enhanced success in achieving adequate arterial flow, however, problems with venous return are becoming more frequent. In traumatic injuries to the extremity, the superficial veins, especially the saphenous system, may receive subacute injuries which are not readily apparent. The deep vena comitans is often a better choice even if an interpositional vein graft must be used to bypass a damaged or fibrotic segment.

The applications of this new technique to difficult reconstruction problems are unlimited. As outlined previously, segmental losses of bone in the mandible, radius, or tibia can be replaced. If there is as associated soft tissue loss, a composite osteocutaneous flap may be employed. Composite musculocutaneous flaps can be successfully transplanted, immediately revascularized, and subsequently reinnervated. Segments of gastrointestional composite tissue can be employed in the successful reconstruction of the cervical esophagus.

The advantages of this new operative procedure are many.

1) Reconstruction can be completed in a single operative procedure. In the treatment of head and neck malignancies, both extirpation and reconstruction can be accomplished during the same anesthetic.

2) The procedure, though lengthy initially, has been shortened appreciably as more experience is obtained.



FIGS. 4a–e. (a) Intraoperative photograph demonstrating defect right forearm resulting from shotgun wound. (b) Intraoperative photograph demonstrating gracilis myocutaneous flap on vascular pedicle prior to transplantation. (c) Intraoperative photograph demonstrating fasicular nerve graft to median nerve. (d) Intraoperative photograph demonstrating revascularization of gracilis myocutaneous flap at recipient defect. (e) Early postoperative result.

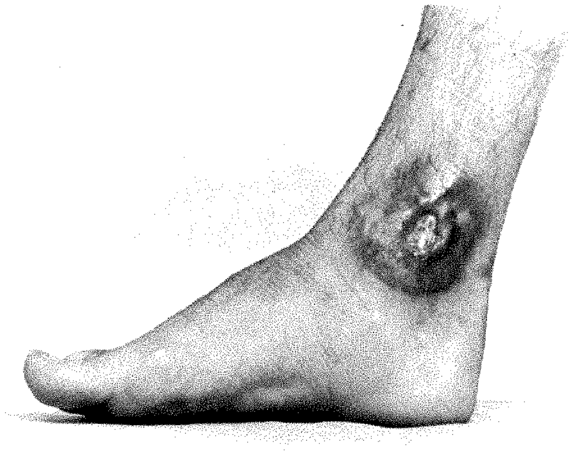


FIG. 5a. Preoperative photograph of chronic draining ulceration lower extremity with bone and tendon exposed subsequent to compound fracture.

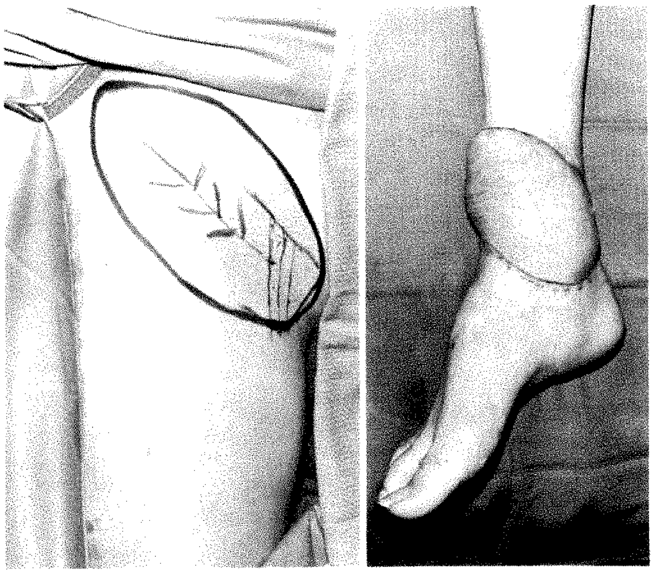
Frequently, the operative procedure can now be completed in four and one-half to six hours.

3) The number of general and local operative procedures required to achieve the desired functional and cosmetic result is considerably less than older existing methods of reconstruction.

4) The total number of hospital days are reduced.

5) The total cost to the patient is similarly reduced reflecting the shortened hospital stay and reduced number of operative procedures.

6) Immobilization is significantly reduced with early ambulation encouraged. The discomfort and restriction of pedicle attachment are eliminated. This is reflected in decreased patient morbidity and mortality statistics.



FIGS. 5b and c. (b, left) Intraoperative photograph demonstrating outline of vascularized groin flap. (c, right) Late postoperative photograph.

7) Composite tissue of varied histological type can be transplanted in a single operative procedure thus eliminating the necessity for secondary operative procedures (*e.g.* osteocutaneous or myocutaneous composite tissue).

8) Finally, reconstruction previously deemed inadvisable with older methods can now be undertaken with reasonable estimates of success. Extremities destined for amputation can now be salvaged, enhancing the quality of life.

The disadvantages of this new operative procedure are few. Some reflect inexperience with a new operative procedure.

1) Specialized training in microsurgery is required as well as a broad surgical background. Failures, when they occur, are most frequently related to improper preoperative and intraoperative planning. Problems of anastomotic patency are secondary and merely reflect these planning errors.

2) A specialized double team of surgeons is required to expedite and facilitate the operation. Because of the specialized skill and necessity for a team approach, the procedure is frequently limited to large medical institutions where these teams are more readily available.

3) Sophisticated equipment, operating microscopes, and instruments are desirable. Although not prohibitively expensive, they are not readily available in most hospitals.

4) Finally, since fine motor skills require repetitive training, an active experimental laboratory is an essential supplement to the clinical experience.[18] A successful laboratory requires adequate space, continued financial support, and a dedicated research team, often limiting it to a larger institution.

Conclusions

Microsurgical composite tissue transplantation is presented as a new method of reconstruction in 69 patients. The versatility of this new operative procedure is discussed and contrasted to older, existing methods of reconstruction. Results compare favorably to these methods, making the newer one the procedure of choice in the reconstruction of extensive defects.

References

1. Acland, R. D.: Thrombus Formation in Microvascular Surgery: An Experimental Study of the Effects of Surgical Trauma. Surgery, 73:766, 1973.
2. Acland, R. D.: Instrumentation for Microsurgery. Ortho. Clin. North Am. 8(2) 281, 1977.
3. Acland, R. D.: Factors which influence success in microvascular surgery. *In* Serafin, D. and Buncke, H. J., Jr., (eds.) Micro-

surgical Composite Tissue Transplantation. St. Louis,Mosby, in press.

4. Chen, C. W.: Replantation of severed limbs and fingers. Chinese Med. J. (N.S.)1:3, 1973. (See also 85:79, 1966).
5. Harii, K., Ohmori, K. and Ohmori, S.: Successful Clinical Transfer of Ten Free Flaps by Microvascular Anastomosis. Plast. Reconstr. Surg., 53:295, 1974.
6. Harii, K., Ohmori, K. and Torii, S.: Free Gracilis Muscle Transplantation with Microneurovascular Anastomosis for the Treatment of Facial Paralysis. Plast. Reconstr. Surg., 57:133, 1976.
7. Horn, J. S.: Reattachment of Severed Forearm. Lancet, 1:1152, 1964.
8. Ikuta, Y.: Skeletal muscle transplantation in the severely injured upper extremity. In Serafin, D. and Buncke, H. J. Jr. (eds.) Microsurgical Composite Tissue Transplantation St. Louis, Mosby, in press.
9. Jacobson, J. H. and Suarez, E. L.: Microsurgery in Anastomosis of Small Vessels. Surg. Forum, 11:243, 1960.
10. Kleinert, H. E. and Kasdan, M. L.: Anastomosis of Digital Vessels. J. Ky Med. Assoc. 63:106, 1965.
11. Komatsu, S. and Tamai, S.: Successful Replantation of a Completely Cut-off Thumb. Plast. Reconstr. Surg., 42:374, 1968.
12. Krizek, T. J., Tani, T., Desprez, J. D., et al.: Experimental Transplantation of Composite Grafts by Microsurgical Vascular Anastomoses. Plast. Reconstr. Surg., 36:538, 1965.
13. Malt, R. A. and McKhann, C. F.: Replantation of Severed Arms. JAMA, 189:716, 1964.
14. McLean, D. H. and Buncke, H. J.: Autotransplant of Omentum to a Large Scalp Defect with Microsurgical Revascularization. Plast. Reconstr. Surg., 49:268, 1972.
15. O'Brien, B. McC., Morrison, W. A., Ishida, H., et al. Free Flap Transfer with Microvascular Anastomosis. Br. J. Plast. Surg., 27:220, 1974.
16. Östrup, L. T. and Fredrickson, J. M.: Reconstruction of Mandibular Defects After Radiation Using a Free Living Bone Graft Transferred by Microvascular Anastomoses. Plast. Reconstr. Surg., 55:563, 1975.
17. Serafin, D. and Georgiade, N. G.: Microsurgical Composite Tissue Transplantation: A New Method of Immediate Reconstruction of Extensive Defects. Am. J. Surg., 133:752, 1977.
18. Serafin, D., Georgiade, N. G. and Morris, R. L.: A Laboratory Manual of Microvascular Surgery, Seeman Division of Fisher-Harrison Corporation, Durham, N.C. 1977.
19. Serafin, D., Georgiade, N. G. and Peters, C. R.: Microsurgical Composite tissue transplantation. Clin. Plast. Surg., 3: No. 3, 447, 1976.
20. Serafin, D., Georgiade, N. G. and Smith, D. H.: Comparison of Free Flaps with Pedicled Flaps for Coverage of Defects of the Leg or Foot. Plast. Reconstr. Surg., 59: No. 4, 492, 1977.
21. Serafin, D., Shearin, J. C. and Georgiade, N. G.: The Vascularization of Free Flaps. Plast. Reconstr. Surg., 60: No. 2, 233, 1977.
22. Serafin, D., Villarreal-Rios, A. and Georgiade, N. G.: Fourteen Free Groin Flap Transfers. Plast. Reconstr. Surg., 57:707, 1976.
23. Serafin, D., Villarreal-Rios, A. and Georgiade, N. G.: A Rib-Containing Free Flap to Reconstruct Mandibular Defects. Br. J. Plast. Surg., 30:263, 1977.
24. Shearin, J. C., Serafin D. and Georgiade, N. G.: Microvascular Anastomosis: An Experimental Model Utilizing the Rabbit Ear. Plast. Reconstr. Surg., 58:454, 1976.
25. Strauch, B. and Murray, D. E.: Transfer of Composite Graft with Immediate Suture Anastomosis of its Vascular Pedicle Measuring Less Than one millimeter in External Diameter Using Microsurgical Technique. Plast. Reconstr. Surg., 40:325, 1967.
26. Tamai, S.: Free muscle transplantation with micro-neuro-vascular anastomoses. *In* Serafin, D. and Buncke, H. J. Jr. (eds.) Microsurgical Composite Tissue Transplantation St. Louis, Mosby, in press.

DISCUSSION

DR. MAURICE J. JURKIEWICZ (Atlanta, Georgia): One of the problems attendant upon the introduction of a new technique or a new procedure is the evangelical zeal that often will tend to extend the indications for a particular therapeutic modality. Free flap transfer is no exception.

Therefore, we are indebted to Drs. Serafin and Georgiade not only for bringing the potential of this procedure to the attention of this Association, but also for attempting to put the procedure in perspective.

They are to be congratulated for a very low failure rate. Harii, of the Tokyo Metropolitan Police Hospital, has reported a series of about 200 cases with a partial failure rate of 13%, and a total failure rate of 13% as well.

In our own institution, we have a very small series of 18 cases in this past year. Our failure rate is 6–7%. We have concentrated on the use of transplanted gut, omentum, and compound flaps.

The point I wish to develop is that in most instances there are options available to the surgeon in achieving functional wound closure or reconstruction. For example, in about 1960 there was a flurry of activity in transfer of revascularized gut up to the neck for reconstruction of the cervical esophagus. I was no exception, and participated in that flurry.

Nakayama, of Japan, had a series of approximately 50 cases of free colon grafts to the neck, with anastomosis to the neck vessels.

Subsequent to that, Bakamjian developed his straight-forward reconstruction of the gullet using a flap of the chest wall, based on the internal mammary vessels—the deltopectoral flap. As a result free transfer of the gut virtually disappeared.

It did so because Bakamjian's technique is reliable. Now, however, with new instrumentation, new suture material, and better control in free flap transfer, we are now again reexamining that particular operative capability of reconstructing the gullet. The time has come, not so much to see how many of these we can do, but, rather, to set up a prospective randomized study to compare a standard reconstructive effort to free composite transfer.

DR. MICHAEL E. JABALEY (Jackson, Mississippi): Doctors Serafin, Georgiade, and their coworkers have compiled the largest and most varied series of free flaps performed in America and with the highest rate of success. In his presentation, Dr. Georgiade states that one of the principal advances of this decade of reconstruction has been the availability of microsurgery. I would submit that perhaps *the* major advance in reconstruction has been a better understanding of the functional blood supply of composite tissue. Dr. Georgiade has shown you some beautiful examples of this understanding. These techniques include but are by no means limited to transfers of skin, bone, nerve, muscle, and the gastrointestinal tract.

Because of this new information, as well as better instrumentation and magnification, reconstructive surgeons now have available techniques which permit a variety of operative choices in problems which heretofore have either been impossible to manage or soluble only be a series of operations strung out over a long period of time and accompanied by great expense.

It is now incumbent on workers in this field to recognize that, simply because the techniques and technology are available, that microvascular transfers are not always the best way to go. We must, as has already been suggested, compare these procedures with other available techniques, such as some of the composite skin and muscle transfers that you have see earlier today.

It is critical to understand that whatever technique we use to transfer the tissue we want to a recipient area, once it is there and healed, it behaves as any other flap. For this reason, we must compare it to tissues available from other areas. For example, in the floor of the mouth or on the neck, on the chest wall, and on the dorsum of the hand and the leg—we must compare the tissue of the reconstruction with that which is available from other areas. The technique which is selected for any reconstruction should be the one which provides the best functional and aesthetic result.

I would like to ask the authors in their discussion if they would tell us, based on the functional capability of the tissue once in place, whether they would elect this procedure, as opposed to some of the others which might be available. And I would ask them specifically about these four areas; the oral cavity, the breast, the hand and forearm, and the lower extremity.

Dr. E. F. Shaw Wilgis (Baltimore, Maryland): About a year ago, in a nationwide survey of the members of the American Society for Surgery of the Hand, we gathered together a large series of free microvascular repairs, including 296 replantations of digits, with a 70% success rate, 45 digital transfers, including toe/thumb and toe/finger transfers, with an overall success rate of about 80%, 56 free skin flaps to the hand, with a similar success rate, 18 free bone flaps, and four free muscle flaps.

I think that this demonstrates the surgical ingenuity which has been generated by this particular modality of microvascular surgery.

There are two questions that I have for the authors. One pertains to the postoperative management and anticoagulation, and what anticoagulation would be used. We personally use nothing but aspirin.

Secondly, in certain types of individuals, like black people, it's very difficult for us to determine the viability of the flap; and we have tried various ways to watch these flaps postoperatively, including clinical assessment, Doppler listening to the vessels, radionuclide angiography, and thermography. I don't think today we have a suitable postoperative management system, and I want to know from the authors if they have been using any particular method, such as fluorescein, or perhaps something more innovative.

Dr. Donald Serafin (Closing discussion): Dr. Warren, I promise not to show any more slides. I would very much like to thank Dr. Jurkiewicz, Dr. Jabaley, and Dr. Wilgis for their discussions, but I would also like to especially thank my Chairman and Associate, Dr. Nicholas Georgiade for his continuing support, and particularly for his technical assistance during the early cases of this series, which were done while I was his resident.

Dr. Jurkiewicz, we are evangelical. There's no question about it. Let me try to respond to some of your very pointed criticism, which I feel has brought several important questions to bear.

We do, indeed, need prospective studies. We have, however, attempted to compare our tissue survival statistics to older existing methods of reconstruction in a recent article published in *Plastic and Reconstructive Surgery* 59:492, 1977. In this retrospective review we have not only looked at flap survival but the length of hospitalization, and other factors that we feel are extremely important in evaluating a new surgical procedure. I feel that we do, indeed, need a prospective study.

Dr. Jabaley mentioned the fact that we needed to further increase our technology. Changes in instrumentation are occurring each day. With increased technology we can become more sophisticated in our approach, permitting us to do things which heretofore were not possible. He also asked, if we would compare the quality of our transferred tissue to other methods and employing local tissue, particularly in reference to the oral cavity, the breast, the hand, and the lower extremity.

How many of you in this audience have transferred a nonvascularized rib, and found that within six weeks—six months—this rib totally disappeared? It was totally resorbed, because the quality of the recipient bed was not suitable; and that the transferred bone, whether it be rib or iliac crest, failed in its reconstructive attempt.

With this new method that we're advocating, the vascularized rib not only was not resorbed, but evidenced good callus formation. I challenge you to show good callous formation and lack of resorption by any existing method of reconstruction.

How many of you have attempted to reconstruct a severely irradiated chest, as was presented in that individual with recurrent chest wall carcinoma, and found that the flap that was transferred to the severely radiated area ultimately failed because of poor vascularity in the recipient bed?

How many of you gentlemen actually transferred a flap, to find that after lengthy and multiple delays, if your patient did not suffer the severe morbidity associated with his prolonged hospitalization —how many of you found that the flap, when it finally arrived at its final destination, was fibrotic and probably deficient in the amount of tissue?

How many of you would be able to excise an extensive squamous carcinoma of the hand, immediately reconstruct the defect, and avoid joint and shoulder contracture by early mobilization as we did in the 80-year-old cartoonist presented?

Finally, Dr. Wilgis' question relating to anticoagulation. Our anticoagulation regimen is quite simple. We do not use heparin in our transplants; neither do we do it in our replantations. We place the patient on aspirin and Persantine preoperatively and continue it postoperatively for two weeks. Low molecular weight dextran is begun intraoperatively and continued for three to five days.

Postoperative viability monitoring, Dr. Wilgis—I share your dismay, and I share your problems. We to date do not have good methods to monitor this tissue postoperatively.

Note the particular difficulty involved in assessing the viability of transplanted rib or muscle now covered by the overlying skin. In our laboratory, working in collaboration with Frans F. Jöbsis, Professor of Physiology, employing his technique of reflected light spectrophotometry, we hope to solve some of the problems of tissue monitoring, and providing important data dealing with flap physiology as well.

Finally, working with the Department of Biomedical Engineering at the University of Seattle, we are developing a buried transducer probe, so that we might carefully monitor the patency of the anastomosis postoperatively in the recovery room.

In the remaining last few minutes, I would like to place our present contribution in its proper historic perspective, as has been requested by our discussants.

On April 23, 1906 Nobel Laureate Alexis Carrel presented his manuscript, "The Surgery of Blood Vessels" before the Johns Hopkins Medical Society. In this historic presentation, he commented on the many new aspects of vascular and transplantation surgery, which today has provided the basis for ideas and techniques.

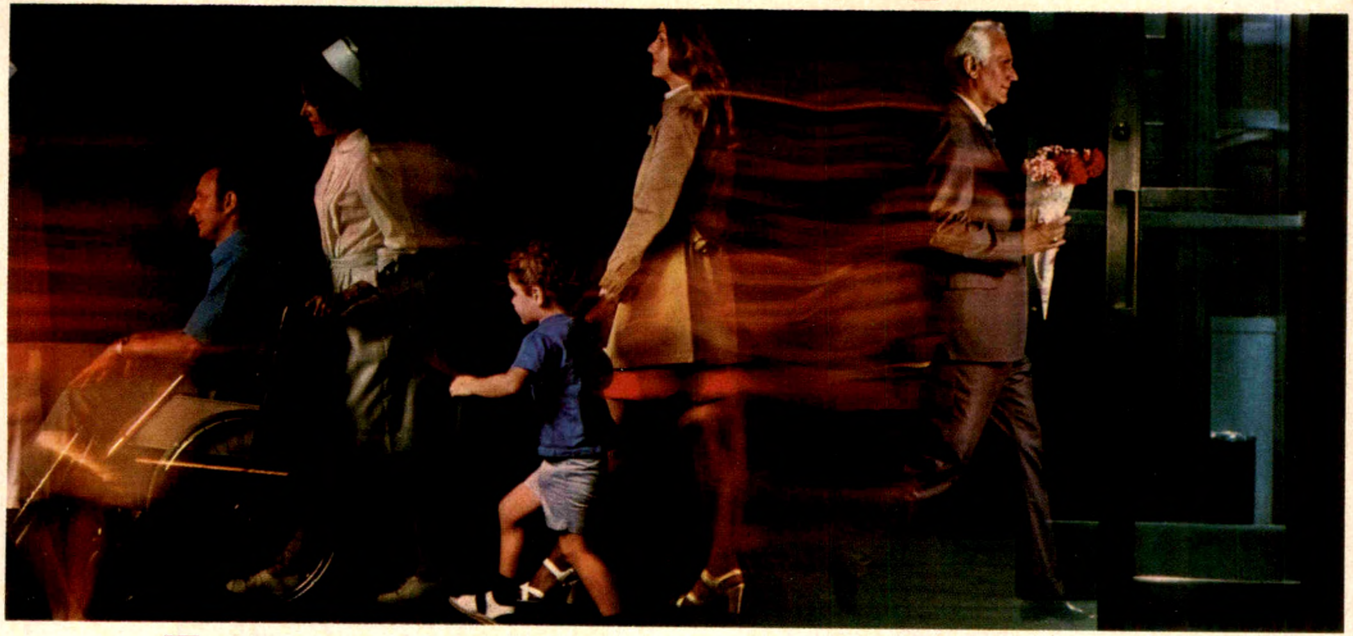
The triangulation technique employed in vascular anastomosis, and the interpositional vein and artery graft, represent only a few of these contributions. He later went on to successfully transplant canine kidneys, limbs, and portions of the scalp.

Seventy years have elapsed since these early contributions. We now have sophisticated operating microscopes, delicate microsurgical instruments, and 11-0 suture on a 50 micron needle. The rapidly expanding subspecialty of microsurgery is still in its infancy, however. Each day brings additional refinements in technique and application, which transcends a single subspecialty.

Efforts in the laboratory must continue to be coordinated with our clinical experience, and solutions to perplexing problems eventually found.

I would like to conclude the discussion today with the following quotation: "The future of transplantation of organs for therapeutic purposes depends on the feasibility of heterotransplantation. Researchers must be directed along this line. But as yet we have not been able to do more than perform a few preliminary experiments." Alexis Carrel, April 23, 1906.

Every day, healthy people leave the hospital– carrying resistant staph.



Today, more than 80%* of community staph is resistant to penicillin G.

Treat these resistant staph infections as effectively in the office as you do in the hospital.

Prostaphlin®
(oxacillin sodium)

*Ross, S. *et al.*: JAMA *229*: 1075 (Aug. 19) 1974.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Prostaphlin® (oxacillin sodium)
Capsule and Oral Solution (11) PROSTAPHLIN 9/11/75

For complete information, consult Official Package Circular.

Indications: Although the principal indication for oxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to oxacillin sodium should be performed.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of oxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to oxacillin sodium, the physician is advised to continue therapy with a drug other than oxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Oxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A previous hypersensitivity reaction to any penicillin is a contraindication.

Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

The possibility of bacterial and/or fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Experience in premature and newborn infants is limited. Caution should be exercised in administration of the drug to such patients and frequent evaluation of organ system function is recommended.

Safety for use in pregnancy has not been established.

Adverse Reactions: The hypersensitivity reactions reported are skin rashes, urticaria, serum sickness and anaphylactic reactions. Oral lesions such as glossitis and stomatitis have been reported. Fever, eosinophilia, oral and rectal moniliasis have also been reported. Hemolytic anemia, transient neutropenia with evidence of granulocytopenia or thrombocytopenia, neuropathy, and nephrotoxicity (oliguria, albuminuria, hematuria, pyuria, and/or cylindruria) are infrequent and usually associated with high doses of parenteral penicillin.

In some newborns and infants receiving high doses of oxacillin sodium (150 to 175 mg./Kg./day), transient hematuria, albuminuria, and azotemia have been encountered. Although the causal relationship is not entirely clear, infants and newborns treated with high doses of the drug should be observed closely for signs of renal impairment.

One patient developed granulocytopenia while receiving intravenous oxacillin sodium and vancomycin. The blood count returned to normal after both drugs were discontinued. Another patient was reported to have leukopenia during intravenous therapy with oxacillin sodium. These counts were made while the patient was moribund. Thrombophlebitis has occurred in a small percentage of patients after intravenous therapy.

Usual Oral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Administer on empty stomach for maximum absorption.

Usual Parenteral Dosage: Adults: 250 to 500 mg. q.4h. or q.6h. Children: 12.5 mg./Kg./q.6h. Children weighing 40 Kg. or more should receive the adult dose.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

Supplied: Capsules—250 and 500 mg. in bottles of 48 and 100. Injectable—250 mg., 500 mg., 1 Gm., 2 Gm., and 4 Gm. dry filled vials for IM/IV use. For Oral Solution —100 ml. bottles, 250 mg./5 ml. when reconstituted.

A.H.F.S. Category 8:12.16

BRISTOL®
BRISTOL LABORATORIES
Division of Bristol-Myers Co.
Syracuse, New York 13201

When did you last hear 'rave reviews'- for an intraperitoneal irrigation agent?

e were satisfied that kanamycin was not ly safe, but also effective in improving rvival in the presence of peritoneal connination." —Nelson, J.L., et al.: Symposium on Surgical Infections and Antibiotics, Surg. Clin. of N.A. 55:6, pages 1391-1395, (December) 1975.

anamycin has been employed in 128 tients at the time of operation for intraritoneal contamination of various types. ere has been no evidence of toxicity m this use of kanamycin."
hn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

ider usage of intraperitoneal kanamycin advocated when intraperitoneal antibi c therapy is indicated." —Cohn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

"...immediate operative use of intraperitoneal antibiotic treatment has lowered the incidence of complications and mortality by 42%." —Clowes, G.H.A.: Forum on Peritonitis, Mod. Med. 40:153 (Apr. 17) 1972.

...our choice at the operating table is kanamycin..." —Clowes, G.H.A.: Forum on Peritonitis, Mod. Med. 40:153 (Apr. 17) 1972.

"Intraperitoneal kanamycin therapy is strongly advocated for any patient with peritonitis." —DiVicenti, F.C., and Cohn, I., Jr.: Am. Journ. Surg. 111:1, pages 147-153, (June) 1965.

"In peritonitis, intraperitoneal administration of kanamycin can be recommended..."
—Pissiotis, C.A., et al.: Surg. Gynecol. Obstet. 134:995 (June) 1972.

Kantrex®

ANAMYCIN SULFATE

a known quantity

BRISTOL™ BRISTOL LABORATORIES
Div. of Bristol-Myers Compan
Syracuse, New York 13201

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Kantrex® Injection and Pediatric Injection

(kanamycin sulfate injection)

(13) 2/28/78

For complete information, consult Official Package Circular.

WARNING:

The major toxic effect of parenterally administered kanamycin sulfate is its action on the auditory portion of the eighth nerve. High frequency deafness usually occurs first and can be detected by audiometric testing. Tinnitus or vertigo may occur and are evidence of vestibular injury and impending bilateral irreversible deafness.

In patients with impaired kidney function, the risk of severe ototoxic reactions and permanent deafness is sharply increased. In such cases, the daily dosage should be reduced and the interval between doses lengthened. If there is evidence of progressive renal dysfunction (increasing NPN, BUN, creatinine or oliguria) during therapy, audiometric tests are advised and discontinuation of the drug should be considered.

Older patients and patients receiving a total dose of more than 15 Gm. of kanamycin sulfate should be carefully observed for signs of eighth nerve damage.

Infants and children generally tolerate the drug well; and when the recommended precautions are followed, the incidence of toxic reactions is low.

Neuromuscular paralysis with respiratory depression may occur when kanamycin sulfate is administered intraperitoneally concomitantly with anesthesia and muscle-relaxing drugs. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug.

The concurrent systemic use of other ototoxic and/or nephrotoxic drugs, particularly streptomycin, polymyxin B, polymyxin E (colistin), neomycin, gentamicin, and viomycin should be avoided.

The administration of kanamycin sulfate and rapid acting diuretic agents, e.g. ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, and mannitol (particularly when the diuretic is given intravenously) may cause irreversible deafness. Concurrent use of these agents should be avoided. (See "Adverse Reactions".)

Usage in Pregnancy

Safety of this drug in human pregnancy has not been established.

CONTRAINDICATIONS:

A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other potentially ototoxic agents may be a contraindication if effective, alternative therapy is available.

THIS DRUG IS **NOT** INDICATED IN LONG-TERM THERAPY (e.g. Tuberculosis) BECAUSE OF THE OTOTOXIC HAZARD WITH EXTENDED ADMINISTRATION.

WARNING:

See "Warning" box above.

PRECAUTIONS:

Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occurs, discontinue therapy. Mycotic or bacterial superinfection may occur.

ADVERSE REACTIONS:

Nephrotoxicity—albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity—see box warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

DOSAGE AND ADMINISTRATION:

The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult total daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gm.

The intravenous route is used only if intramuscular administration is not feasible. The 500 mg. dose is added to the 200 ml. of sterile diluent and administered 60 to 80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

As aerosol treatment, 250 mg. of Kantrex is diluted with 3 ml. of physiological saline and nebulize.

Kantrex Injection in concentrations of 0.25 per cent (2.5 mg./ml.) has been used satisfactorily as an irrigating solution in abscess cavities, pleural spaces, peritoneal and ventricular cavities.

SUPPLIED:

Rubber capped vials as a ready-to-use sterile aqueous solution in two concentrations:

KANTREX INJECTION (kanamycin sulfate injection)
NDC 0015-3502-20—500 mg. per 2 ml.
NDC 0015-3502-24—Disposable Syringe (500 mg. per 2 ml.)
NDC 0015-3503-20—1.0 Gm. per 3 ml.
KANTREX PEDIATRIC INJECTION (kanamycin sulfate injection)
NDC 0015-3512-20—75 mg. per 2 ml.
(activity assayed as kanamycin base)

BRISTOL™ BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

PRESERVE and PROTECT YOUR COPIES OF ANNALS of SURGERY

Now, your journals can become a handsome addition to your professional library.

These file boxes are designed and custom-made to keep your copies orderly, readily accessible and clean.

Durable book-binder's board covered with scuff-resistant, washable Leathertex. Lettering embossed in 23-Karat gold leaf.

Jesse Jones Box Corp. (since 1843)
Dep't. JBLA—Phila., Pa. 19141

Gentlemen: Kindly send me:

Reasonably priced, too. Only $4.95 ea. ☐

3 for $14.00 ☐ 6 for $24.00 ☐

Add $1.00 postage per file for orders outside the U.S.

☐ Check enclosed (Make check payable to: Jesse Jones Box Corp., Box 5120, Phila., Pa. 19141)

Name ____________________

Address ____________________

City/State/Zip ____________________

Shipped postpaid U.S. only. Satisfaction unconditionally guaranteed or your money back.

Reliable and safe hemostat

to help control small-vessel bleeding without injuring vital tissue

SURGICEL

TRADEMARK

Absorbable Hemostat

(oxidized regenerated cellulose)

SURGICEL Absorbable Hemostat
TRADEMARK
(oxidized regenerated cellulose)

FOR SURGICAL USE

(For dental applications of this product, reference should be made to the package insert for dental use.)

DESCRIPTION: SURGICEL Absorbable Hemostat is a chemically-sterilized, absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and can be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance.

ACTIONS: The mechanism of action whereby SURGICEL accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors including the amount used, degree of saturation with blood, and the tissue bed.

INDICATIONS: SURGICEL Absorbable Hemostat (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective.

CONTRAINDICATIONS: Although packing or wadding sometimes is medically necessary, SURGICEL Absorbable Hemostat should not be used in this manner unless it is to be removed after hemostasis is achieved.

SURGICEL should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

When SURGICEL is used to help achieve hemostasis around the spinal cord in laminectomies, or around the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure.

SURGICEL should not be used to control hemorrhage from large arteries.

SURGICEL should not be used on *non-hemorrhagic serous oozing surfaces,* since body fluids other than whole blood, such as serum, do not react with SURGICEL to produce satisfactory hemostatic effect.

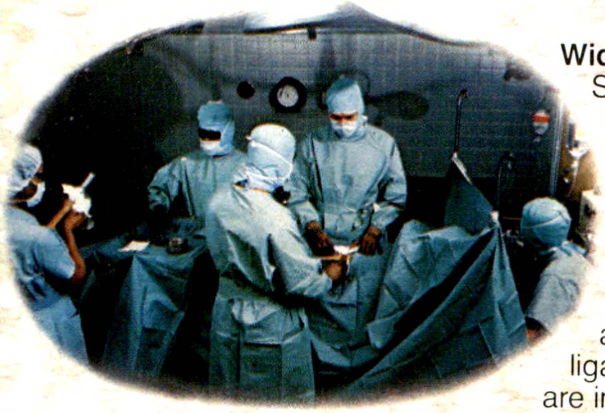
WARNINGS: SURGICEL Absorbable Hemostat is supplied sterile and should not be autoclaved because autoclaving causes physical breakdown of the product.

SURGICEL is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

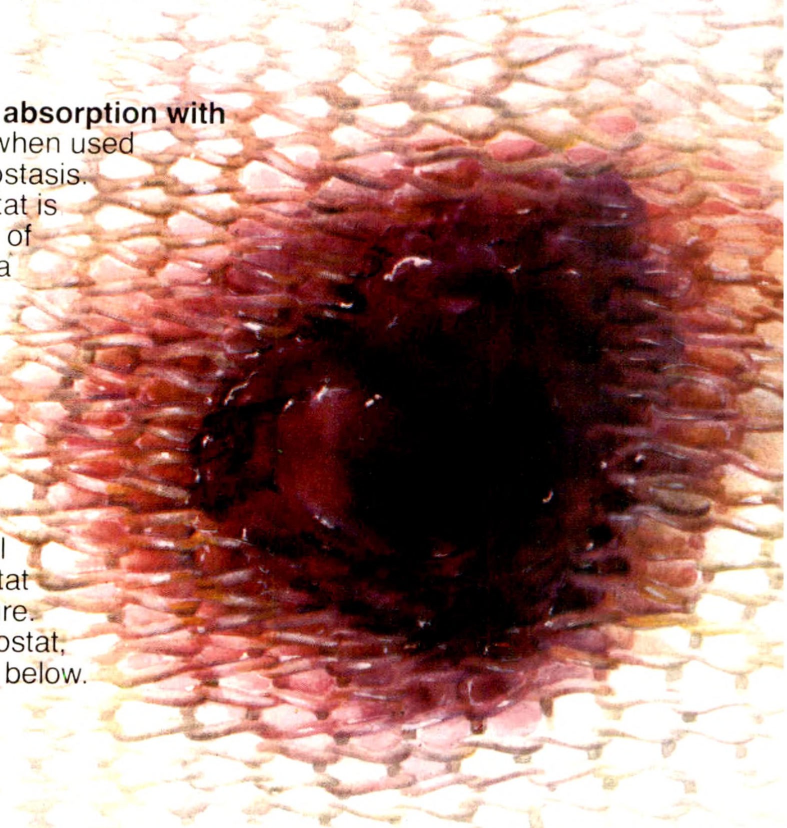
Closing SURGICEL in a contaminated wound without drainage may lead to complications and should be avoided.

The hemostatic effect of SURGICEL is

©Johnson&Johnson 1975



Wide hemostatic application in surgery. SURGICEL* Absorbable Hemostat is a pliable knitted fabric that has been found to be inherently and dependably hemostatic when used as an aid in the control of small-vessel bleeding in abdominal, thoracic, neurosurgical, orthopedic, cardiovascular, gynecologic and otorhinolaryngologic procedures, in superficial open wounds and on donor sites. SURGICEL Absorbable Hemostat is a valuable adjunct in the control of small-vessel bleeding when ligation or other conventional methods of control are impractical or ineffective.



Rapid and complete absorption with virtually no tissue reaction when used properly in minimal amounts for hemostasis. SURGICEL Absorbable Hemostat is completely absorbable from sites of implantation after it has become a gelatinous mass that aids in the formation of a clot.

Convenient to use. SURGICEL Absorbable Hemostat requires no additional hemostatic preparation; it is ready for use directly from the vial. When exposed to blood, it adheres readily to tissues but generally not to dry instruments or dry surgical gloves. SURGICEL Absorbable Hemostat should be stored at controlled room temperature. Before using SURGICEL Absorbable Hemostat, please refer to product information below.

greater when it is applied dry; therefore it should not be moistened with water or saline.

SURGICEL should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved. It *must* always be removed from the site of application after use in laminectomy procedures and from foramina in bone when hemostasis is obtained. This is because SURGICEL, by swelling, may cause nerve damage by pressure in a bony confine. Paralysis has been reported when used around the spinal cord, particularly in surgery for herniated intervertebral disc.

PRECAUTIONS: Use only as much SURGICEL Absorbable Hemostat as is necessary for hemostasis, holding it in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction.

SURGICEL should be applied loosely against the bleeding surface. Wadding or packing should be avoided, especially within rigid cavities, where swelling may interfere with normal function or possibily cause necrosis.

In *urological procedures*, minimal amounts of SURGICEL should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.

Since absorption of SURGICEL could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.

If SURGICEL is used temporarily to line the cavity of large open wounds, it should be placed so as not to overlap the skin edges. It should also be removed from open wounds by forceps or by irrigation with sterile water or saline solution after bleeding has stopped.

Precautions should be taken in *otorhinolaryngologic surgery* to assure that none of the material is aspirated by the patient. (Examples: controlling hemorrhage after tonsillectomy and controlling epistaxis.)

Care should be taken not to apply SURGICEL too tightly when it is used as a wrap during vascular surgery (see "ADVERSE REACTIONS" section).

ADVERSE REACTIONS: "Encapsulation" of fluid and foreign body reactions have been reported.

There have been two reports of stenotic effect when SURGICEL Absorbable Hemostat has been applied as a wrap during *vascular surgery*. Although it has not been established that the stenosis was directly related to the use of SURGICEL, it is important to be cautious and avoid applying the material tightly as a wrapping.

Possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy have been reported. There has been one report of a blocked ureter after kidney resection, in which postoperative catheterization was required.

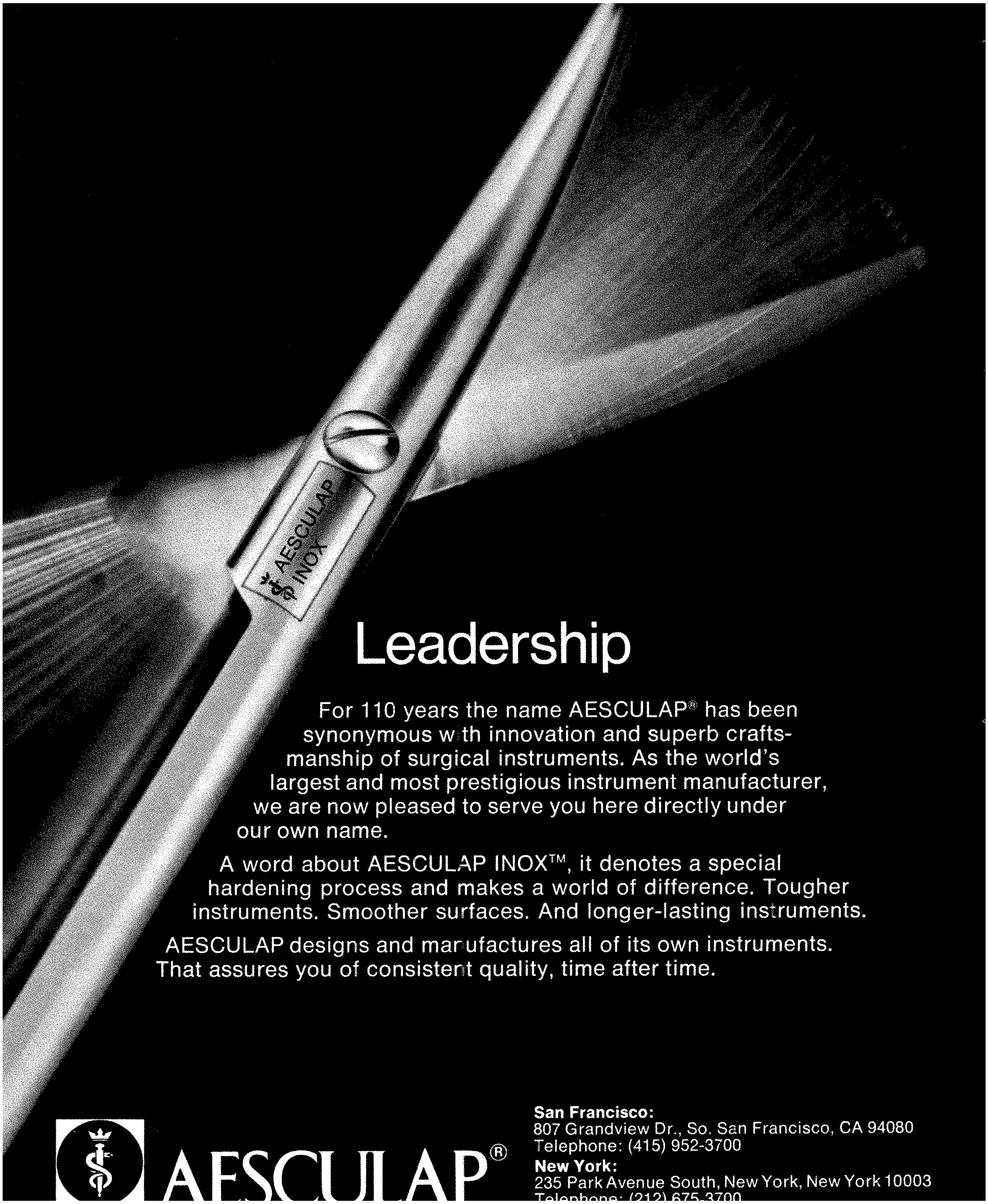
Occasional reports of "burning" and "stinging" sensations and sneezing when SURGICEL has been used as packing in epistaxis, are believed due to the low pH of the product.

Burning has been reported when SURGICEL was applied after nasal polyp removal and after hemorrhoidectomy. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL was applied on surface wounds (varicose ulcerations, dermabrasions, and donor sites) also have been reported.

SURGIKOS
A Johnson & Johnson Company
New Brunswick, New Jersey 08903

---

*Trademark of Johnson & Johnson



Leadership

For 110 years the name AESCULAP® has been synonymous with innovation and superb craftsmanship of surgical instruments. As the world's largest and most prestigious instrument manufacturer, we are now pleased to serve you here directly under our own name.

A word about AESCULAP INOX™, it denotes a special hardening process and makes a world of difference. Tougher instruments. Smoother surfaces. And longer-lasting instruments.

AESCULAP designs and manufactures all of its own instruments. That assures you of consistent quality, time after time.

AESCULAP®

San Francisco:
807 Grandview Dr., So. San Francisco, CA 94080
Telephone: (415) 952-3700
New York:
235 Park Avenue South, New York, New York 10003
Telephone: (212) 675-3700

Esophageal Resection and Replacement for Carcinoma

E. F. PARKER, M.D., J. F. BALLENGER, M.D. AND K. C. SHULL, M.D.

This report covers a review of 77 cases of esophagectomy performed in the Medical University and Roper Hospitals from January 1964 through December 1975. Seventy-two cases had primary carcinoma of the esophagus. The other five had carcinoma primary in the stomach, and had proximal gastrectomy also. All except 9 cases had preoperative x-ray therapy. There were 31 white males, 13 white females, 25 black males, and six black females. Ages ranged from 37 to 73 years of age. Four methods of restoration of continuity of the alimentary canal were used. End-to-end anastomosis was use in one case. The stomach was transplanted into the thorax, and when necessary into the neck in 36; a segment of jejunum was transplanted in 12; and a segment of colon in 28 cases. Deaths and complications are reviewed. Among the 72 cases of carcinoma of the esophagus, 35 had palliative resection, 34 had theoretically curative resection and three were in doubt. There were no two year survivors among the patients having the carcinoma primary in the stomach. Among cases having the carcinoma primary in the esophagus, there have been nine cases with two year survival (12%) and six cases with five year survival (8%). On the basis of our experience, we prefer a single stage operation of laparotomy and right thoracotomy, and the use of the whole stomach placed in the esophageal bed and transplanted into the neck if necessary, except in those cases in whom there has been a previous gastric resection. Generally speaking we have had least trouble with the stomach, more with the colon, and most with the jejunum.

THIS REPORT COVERS a review of 77 cases of esophagectomy performed for malignant disease between January 1964 through December 1975. Of these, 72 had primary carcinoma of the esophagus. The other five had carcinoma primary in the cardia of the stomach invading the distal esophagus, in whom a proximal gastrectomy was also performed. Of the 72 cases having carcinoma primary in the esophagus 70 were squamous celled, and two were adenocarcinoma. We have observed about this proportion of squamous cell to adenocarcinoma in our previous studies of primary carcinoma of the esophagus.[8] Of the five cases having carcinoma primary in the cardia of the stomach, all were adenocarcinoma. The patients were treated in the Medical University and Roper Hospitals. The latter is a private hospital, and the former is a teaching hospital accepting patients by referral, regardless of the ability of the patient to pay.

From the Division of Thoracic Surgery, Medical University of South Carolina and Roper Hospital, Charleston, South Carolina

The ages ranged from 37 to 73 years among the five patients having the carcinoma primary in the cardia of the stomach. In the patients with primary carcinoma of the esophagus, the ages also ranged from 37 to 73 years with the majority (54 cases) in the sixth and seventh decades, 12 cases under the age of 50, and six cases over the age of 70 (Table 1).

The cases consisted of 31 white males, 13 white females, 25 black males, and six black females. These were not the usual proportions of the race and sex among cases of primary carcinoma of the esophagus.[6] The unusual distribution among the 77 cases treated by resection can be explained on the basis of the fact that, broadly speaking, the whites are apt to have less advanced disease and less malnutrition and therefore to be better operative risks (Table 2).

Prior to esophagectomy 65 of the 72 patients having carcinoma primary in the esophagus had preoperative x-ray therapy, (4,500 rads in 18 fractions over a period of three and one-half weeks) which we think is the preferred treatment.[3] Among the seven cases not having had preoperative x-ray therapy, there was one who had emergency operation because of perforation during esophagoscopy and biopsy; one had primary adenocarcinoma of the esophagus in which case it was elected by the attending surgeon not to use it, and there were two cases in whom diagnosis was not made until biopsy at the time of the operation. In the remaining three of the seven cases, preoperative radiation therapy was not used because the attending surgeon elected not to follow our usual protocol for treatment of these cases.

Four methods of restoration of continuity of the alimentary canal were used (Table 3). End-to-end esophageal anastomosis was used in one case after resection of a carcinoma in the cervical esophagus. The stomach was transplanted into the thorax, and when necessary

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Reprint requests: E. F. Parker, M.D., Division of Thoracic Surgery, Medical University of South Carolina, Charleston, South Carolina.

0003-4932-78-0600-0629-0075 © J. B. Lippincott Company

TABLE 1. *Carcinoma of Esophagus and Cardia of Stomach—77 Cases (1964–1975)*

Ages	Primary Stomach	Primary Esophagus
Under 50	1	12
51–60	1	31
61–70	2	23
Over 70	1	6
	—	—
Total	5	72

Range 37–73 years.

into the neck, in 36 cases. A segment of jejunum was transplanted in 12 cases with isoperistaltic anastomosis. A segment of colon was transplanted in 28 cases, in whom we have preferred to use the transverse and descending colon with antiperistaltic anastomosis. The techniques have been described elsewhere.[1-7] The operations have been performed by 16 surgeons, eight of whom were on the attending staffs on one or both of the hospitals and eight of whom were on the resident staff of the teaching hospital.

The operation of end-to-end anastomosis was complicated by disruption with the development of cervico-mediastinal abcess which was drained adequately through the cervical incision but he died at home after a prolonged debilitating illness. We have used end-to-end anastomosis after resection successfully and this was reported in 1949.[5] However, this is the first time we have used it since, and do not recommend it.

Among the 36 cases having a gastric transplantation there were seven deaths (19.4%) (Table 4). These were secondary to unilateral and bilateral pneumonia with respiratory failure in four cases, cardiac complications along with pulmonary in two cases, and an anastomotic breakdown and mediastinitis in one case. There were 12 (36.1%) cases having nonfatal complications. These included atelectasis or pneumonia, or both, in six cases; tachyarrhythmia in three cases; cardiac complications in addition to pulmonary and vocal cord paralysis in one case; a cardiac complication in addition to pulmonary and renal complications in one case; a wound abscess in one case; and bilateral nonsuppurative pleural effusion in the remaining patient among the 13 cases. There were no complications in the remaining 16 cases (44.4%) among the 36 having replacement of the esophagus by transplantation of the whole stomach. In this series there were no cases having creation and transplantation of a gastric tube from the greater curvature. However, we have used the reversed gastric tube in other cases and we have observed leaks and perforations from the tube, with empyema and death, and therefore we are not enthusiastic about its further use. Except in children we see very little if any advantage in the use of the reversed gastric tube over the whole stomach. Among late complications after transplantation of the stomach we have seen infrequently cases of gastric ulcer, but these have been managed successfully non-operatively. We have also seen stricture at the site of the proximal anastomosis, presumably due to reflux esophagitis in the distal end of the remaining esophagus, but this has been infrequent and successfully managed by dilatations.

TABLE 2. *Carcinoma of Esophagus and Cardia of Stomach Treatment by Resection (77 Cases)*

White male	31
White female	13
Black male	25
Black female	8

TABLE 3. *Resection and Replacment (77 Cases)**

End-to-end anastomosis	1
Transplantation of stomach	36
Transplantation of jejunum	12
Transplantation of colon	28

* January 1 to December 31, 1975.

Among the 12 cases having transplantation of the jejunum, there were three deaths (25.0%) (Table 4). There was one from massive hemorrhage from a large vein in the suspensory ligament of the left lobe of the liver; another was due to respiratory failure which possibly could have been prevented; the third was due to gangrene of the jejunal segment and empyema. The nonfatal complications numbered six (50.5%). There was no anastomotic leak. There was one case with necrosis of the transplant which required reoperation and replacement with a colic transplant. This patient had operation eight years ago and died in the second year after operation having had good palliation. There were four others with complications mainly cardiac or pulmonary. There were only three cases with no complications (25.0%).

Because of the tenuous blood supply of the jejunum in many cases, and because of our high morbidity and mortality rates with its use, we have almost completely abandoned the use of the jejunum. In an occasional patient, usually with benign disease, who needs only a short segment transposed into the inferior medias-

TABLE 4. *Complications of Esophagectomy*

	Stomach	Jejunum	Colon
Fatal	7 (19.4%)	3 (25%)	4 (14.3%)
Nonfatal	13 (35.1%)	6 (50%)	17 (60.7%)
None	16 (44.4%)	3 (25%)	7 (25%)

tinum, we use an isoperistaltic segment. This would be particularly applicable to children. In children the intrathoracic stomach without an effective antireflux mechanism could lead to serious problems with esophagitis and the possible complications of ulcer, hemorrhage, and stricture. When one considers that the colon after transplantation regains no effective peristalsis and acts merely as a conduit[4] and the fact that the jejunum regains function, it makes the jejunum most desirable for replacement of the esophagus, but the nature of its blood supply has also sharply limited its usefulness in our hands.

Among the 28 cases having replacement of the esophagus by transplantation of the transverse and descending colon, there were four deaths (14.3%) (Table 4). There was one due to infarction of the colon, despite re-operation and replacement with the stomach. There was also an anastomotic leak. Another died of supraventricular tachycardia. Another died with empyema and septicemia without a demonstrable leak in the anastomosis. Nonfatal complications occurred in 17 cases (60.7%). These were mainly cardiopulmonary. There were no complications in the remaining seven (25%) of the 28 cases.

We have felt that the colon had its maximal usefulness when esophageal bypass was indicated preliminary to thoracotomy for esophagectomy. In such cases the transplanted segment of colon has been placed in the anterior mediastinum between the divided cervical esophagus and the stomach. However, more frequently we have placed the colic segment in the esophageal bed. The use of the colon has also been clearly indicated in patients who had previous gastric resection, usually for peptic ulcer disease.

There was residual carcinoma in the surgical specimen in 25 of the 28 cases (90%) treated between 1968 and 1975. In another study, there was a 97% incidence of residual carcinoma in the surgical specimens in 101 patients treated by resection after preoperative x-ray therapy in the same institutions, as reported by Marks et al.[3]

The extent of the tumor was classified as local and if there was no extension beyond the esophagus, such as continuity with the posterior wall of the left main bronchus, and if there was no adjacent or regional or distant lymph node involvement. The tumor was classified as regional if there was adjacent lymph node metastasis, or extension of the carcinoma through the wall of the esophagus into continuous tissues, but without distant metastasis. The extent was classified as distant if there were tumor in the liver or lymph nodes around the left gastric artery, the cardiac end of the stomach or in the cervical lymph nodes.

The operation was classed as palliative if it was known that all tumor was not excised. Operation was classed as theoretically curative if all known tumor was excised, including regional sites such as lymph nodes in the carina or other sites in the mediastinum, or around the cardiac end of the stomach or the left gastric artery.

TABLE 5. *Carcinoma of the Esophagus at Time of Laparotomy-Thoracotomy*

Extent		Survivors	
		2 Yr.	5 Yr.
Local	35	7	5
Regional	19	1	0
Distant	13	1	1
Not stated	5		
Total	72	9 (12.5%)	6 (8.0%)

The extent of the lesion in the 72 cases of carcinoma of the esophagus at the time of larparotomy and thoracotomy was local in 35, regional in 19, distand in 13, and not clearly stated in five. Of those having only local involvement there have been seven of 35 (20%) surviving for two years or longer; of those having regional or distant involvement, here have been only two of 32 (6%) surviving for two years or longer (Table 5).

Considering survival, there have been no survivors for as long as two years among the patients having the carcinoma primary in the cardia of the stomach. All five died because of local recurrence or metastasis or both. Three had preoperative x-ray therapy and two did not.

Among 72 cases having the carcinoma primary in the esophagus, there have been five survivors for two years or longer among those having gastric transplantation, the intervals being 13 years, 10 years, four years, two years plus and two years in one case each. One of the two year survivors has just died of hepatitis, without evidence of residual carcinoma. A possible relationship between the development of a fatal hepatitis and removal of the spleen due to accidental injury at the time of operation, remains dubious. The other two year survivor has had excellent palliation with normal swallowing, but now has cervical lymph node and possible cerebral metastases. Among those having colic transplantation there have been long term survivals in four cases, the intervals being 13 years, 11 years, seven years, and six years, in one case each. Thus the two year survivors total nine cases or 12.5%, and the five year survivors total six or 8.0%. However, one of the five year survivors had developed a primary adenocarcinoma of the lung, and another has developed a primary carcinoma of the breast (Table 6).

TABLE 6. *Carcinoma of Esophagus (72 Cases Treated by Resection)*

	Stomach	Jejunum	Colon
Palliative	18	7	10
Theoretically curative	15 (5)	5	14 (4)
Not stated			3

Numbers in ( ) indicate two year survivors.

From the standpoint of survival from carcinoma in contradistinction to survival from the complications of operation, it does not matter what organ is used to replace the esophagus after resection, or even if it is not replaced. However, on the basis of our experience[8] we prefer a single stage operation of laparotomy and right thoracotomy,[2] and the use of the whole stomach placed in the esophageal bed and transplanted into the neck if necessary, except in those cases in whom there has been a gastric resection previously to the extent that insufficient stomach remains, in which case we prefer the use of the colon. Only one anastomosis is necessary in a gastric transplantation. With the others there are more. Generally speaking we have had least trouble with the stomach, more with the colon, and most with the jejunum.

References

1. Clowes, G. H. A., Neville, W. E. and Gregorie, H. B., Jr.: Esophageal resection and replacement with a segment of colon. *In* Cooper, P. (ed) The Craft of Surgery. Vol. 1 Boston, Little, Brown, 1964, p. 148.
2. Lewis, Ivor: The Surgical Treatment of Carcinoma of the Esophagus. Br. J. Surg., 34:18, 1946.
3. Marks, R., Scruggs, H. J. and Wallace, K. M.: Preoperative Radiation Therapy for Carcinoma of the Esophagus. Cancer, 38:84, 1976.
4. Othersen, H. B. and Clatworthy, H. W.: Functional Evaluation of Esophageal Replacement in Children. J. Thorac. Cardiovasc. Surg., 53:55, 1967.
5. Parker, E. F. and Brockington, W. S.: Esophageal Resection with End-to-End Anastomosis Experimental and Clinical Observations. Ann. Surg., 129:588–605, 1949.
6. Parker, E. F., Hanna, C. B. and Postlethwaite, R. W.: Carcinoma of the Esophagus. Ann. Surg., 135:697, 1952.
7. Parker, E. F. and Gregorie, H. B., Jr.: Carcinoma of the Esophagus. Curr. Probl. Surg., April, 1967.
8. Parker, E. F. and Gregorie, H. B.: Carcinoma of Esophagus-Long Term Results. JAMA, 235:1018, 1976.

DISCUSSION

DR. HARRY B. GREGORIE, JR. (Charleston, South Carolina): High mortality and morbidity too often relate to esophageal surgery done as an occasional procedure. I feel very strongly that such operations should be done by a surgeon with a highly developed interest or experience in this subject. In this report, seven of the nine long-term survivors were done by Dr. Parker. Bear in mind, there were 15 other surgeons involved in these cases.

Second, optimal chances of cure of carcinoma of the esophagus reside in early diagnosis and combination therapy. Such therapy consists of preoperative radiation treatment and radical esophagectomy.

Studies of more than 600 cases at our hospital have led to this impression. Ninety-seven per cent of the patients who had resection had residual carcinoma. In addition, careful and vigorous supportive treatment is mandatory pre- and postoperatively, and often involves hyperalimentation.

Third, the faint glimmer of success, as reflected by a few long-term survivors in Dr. Parker's report today, is likely due to his enthusiastic willingness to undertake the care of many patients that others may judge to be hopeless; and I know this very well to be quite true.

Fourth, the colon does perform well for long periods of time as an esophageal substitute. However, for reasons of simplicity and safety, except in upper third lesions or the young patient, I have slowly swung to the use of the stomach.

(Slide) This is a study from our institution by Dr. Marks of the Radiotherapy Department, and, I think, does emphasize that, while there is an occasional survivor, long-term survival from radiation therapy alone is not very good.

(Slide) Now, this draws upon a personal experience in 82 patients over a 16 year span, wherein resection has been done as a single-stage procedure in 86%. Malignant disease has been involved in the majority of these patients. In those having benign disease there has been no operative mortality. Colon has been used most; stomach and jejunum some.

(Slide) In looking at carcinoma of the cardia, there were no patients in which colon was used that achieved long-term survival; the average survival was less than a year. In patients having carcinoma of the cardia, where stomach was used, there are two patients, or 50% of this small group, who have had long-term survival. Both of these patients had early diagnosis.

There is one patient with a carcinosarcoma perhaps headed to long-term survival, and one with a reticulum cell sarcoma alive over ten years later.

Now, where stomach has been used for carcinoma of the esophagus, there are 44% of the patients alive at just over a year and a half. The operative mortality has been about 11%. It is hoped that this figure will get better, as it's been only recently that I have come more to the use of the stomach.

(Slide) Now, in carcinoma of the esophagus, where the colon has been used for transplantation, there are three patients of 31 alive, a 10% survival, averaging now over 15 years, this indicating the long-term survival capacity with the colon.

I'd like to have you focus here, because I think this is the interesting part of this. Among these patients, there was long-term survival in 43% at over eight years, and there were 20% of these patients who died without evidence of recurrence, but lived almost ten years.

Now, I realize that these figures are not particularly significant, because the numbers are too few; but I do think that it says two things: 1) that there is some hope for survival among some of these patients; and also, it pays to have a good teacher.

I'd like to ask Dr. Parker two questions. First, what does he think can be done to improve outcome in this problem? Second, what does he propose as a means of aiding that patient who is incurable at the time of diagnosis, but cannot swallow well?

DR. JOSEPH S. MCLAUGHLIN (Baltimore, Maryland): I believe that Dr. Parker's series represents the finest results attainable with a radical therapeutic regimen for carcinoma of the esophagus.

Seven years ago, my associate, Dr. John Hankins, and I examined the results of the patients with carcinoma of the esophagus treated at the University of Maryland. Approximately 250 patients had been seen during the preceding ten year period. For the most part, these patients were treated by radical resection. The operative mortality rate was completely unacceptable. The five year survival rate in the total group was 2.5%. More important was the fact that far more people were made miserable by therapy than were palliated, let alone cured.

Because of these results, we had a complete change in philosophy. We accepted the fact that carcinoma of the esophagus, with rare exceptions, is an incurable disease. Our primary goal of therapy became palliation, with cure a secondary, if important goal.

(Slide) The treatment plan was relatively simple. For the first five years, in the upper third and cervical region lesions, which are relatively few in number, we tried irradiation therapy. We have now switched to colon bypass in most instances. In middle third and lower third lesions, which by far make up our largest group, we carry out a palliative, or, if you prefer, a limited resection. And we carry it out in all patients who have the potential of surviving the operative procedure, which in our group of patients is about 75–80% of the total. The remaining patients, many of whom have bronchioesophageal fistulae, literally are all dead within a month.

(Slide) This slide takes us up to Winter 1977. We have operated upon 51 patients. The mortality rate was about 10%, and it has continued to be about 10% to the present time. Virtually, every patient operated upon was well palliated, which in this disease simply means that they are able to swallow without pain or discomfort.

Now, if one sets out on a philosophy for palliation, you have to show that you have not jeopardized the possibility of cure in those patients, no matter how few, who have the potential of cure. In fact, our figures show an improvement in survival over what was attained by radical therapy—and in a more inclusive group of patients than were formerly treated.

(Slide) In the group of patients with middle and lower third lesions, 44% of the patients survive one year, which I believe is comparable to the figures shown. The survival is 25% at two years, and at five years 14% of these patients are still alive; and presumably, are completely cured.

Now, as I pointed out at the beginning of my discussion, I believe that Dr. Parker's results (and I would include Dr. Nakayama's results in what I am about to say) are the finest results that one is able to obtain with radical treatment of carcinoma of the esophagus. I believe that our approach provides a clear alternative, and I recommend it to you accordingly.

Dr. Edward F. Parker (Closing discussion): Drs. Gregorie and McLaughlin and I have had discussions about this before. I envy indeed the results of Dr. McLaughlin and his group. We have not been able to obtain a 10% mortality, and I respect indeed their ability; but I somehow think that carcinoma varies in different parts of the world, in different parts of this country and in different races. It fascinates me that eight out of nine of our long-term survivors are white, and the other one is a mulatto, and all nine were private. We have no nonprivate patients who are long-term survivors.

Definitions are difficult at present, with the government interference in the practice of medicine, because now one has to define a private patient as one who has the right of choice of private physician, and sense enough to exercise it, and we have many patients who have the right of choice of private physician, but they are all through our nonprivate clinics. So it's difficult to define privacy on the same basis as we did before.

All of these (long-term survivors) are private patients, patients who were able to meet their obligations, whereas our usual incidence of carcinoma of the esophagus is 86% black, and 14% white. So, you see, there's quite a difference in the survival rate.

In Dr. McLaughlin's group—I don't know how many were white and how many were black and whether or not he has the same problem we have.

Concerning the number who come to operation after x-ray therapy, our operability rate has varied over the years, just between 20–30%. And our resectability rate averages around 70–85%. This shows that, of the 415 cases in the group who had preoperative x-ray therapy, there were 137 cases that were operable, and 101 who were resectable. We have not been able to get as good a survival rate—14% at five years is very excellent, and I certainly commend him. Our operability and resectability rates have improved over the years, but they are still low.

Now, Dr. Gregorie asked what we can do for those people who are inoperable right from the start, and incurable. As Dr. McLaughlin said, it's axiomatic to say that in anyone with dysphagia—there's no successful palliative treatment without restoration of the ability to swallow. That can be done in a high percentage of cases with x-ray therapy.

(Slide) In those who can't swallow, we are beginning to use, for the first time, more endoesophageal instrumentation. Boyce in Tampa and Palmer in New Jersey have used dilatations for years. We have been afraid of it. The tumors are highly friable. They are subject to perforation, to be followed frequently by empyema, and death. We are beginning to use now a Proctor-Livingston tube devised by two men in Durban, South Africa, and such a tube is shown in this slide.

For the future, I don't know what we're going to do about cancer, until we find ways of finding the tumor when it is still localized. And that means we have to have better methods of staging. For carcinoma of the esophagus, it takes three major operations to stage: laparotomy, thoracotomy, and opening one or both sides of the neck, as a rule. We have to find a way to do less than that, because all of these patients are critically ill. Our patients don't stand operation without preliminary treatment with hyperalimentation, as Dr. McLaughlin suggested, and we use it, but we haven't made a controlled study of its ultimate value.

We have considered laparoscopy—the "in" word now for peritoneoscopy—but we have seen too many cases where laparoscopy is not going to reveal retroperitoneal lymph nodes, or metastases deep in the liver. Palpation is also necessary for staging.

The same applies to thoracoscopy, to substitute for open thoracotomy. We would be in the pleural cavity with the thoracoscope; we need to be in the mediastinum.

Dr. Benson Wilcox and his confreres presented an excellent paper recently on mediastinoscopy for staging in these patients with carcinoma of the esophagus, but we find that most of the metastases are in the posterior mediastinum, whereas mediastinoscopy allows access to the anterior mediastinum. So I'm not sure that's the answer either.

We have to have better staging, I think, before we're going to be able to get better results than we are having now.

Spontaneous Rupture of the Esophagus

PANAGIOTIS N. SYMBAS, M.D., CHARLES R. HATCHER, JR., M.D., NICKOLAOS HARLAFTIS, M.D.

Spontaneous rupture of the esophagus remains a medical and surgical challenge. Its diagnosis is often missed or delayed resulting in increased morbidity and mortality, and controversy exists as to the mode of therapy for the cases seen later than 12 hours after rupture. During the last seven years, nine patients were treated at Grady Memorial Hospital. Four patients, "early group," were operated upon within 12 hours from the onset of their symptoms and five, "late group," were operated upon between 20–76 hours (average 41) after rupture. All four patients in the "early group" had primary repair of the rupture and two had, in addition, fundoplication. From the two patients with primary repair alone, one developed postoperative leakage at the esophageal suture line, which closed spontaneously; whereas, in the two patients with fundoplication, no leakage occurred. Three of the four patients recovered and one died from renal failure, gastrointestinal bleeding, and gastric perforation. In the "late group" one patient had T-tube drainage of the esophagus and died. Two had primary repair alone with one death and the other two had primary repair with fundoplication 20 and 76 hours postrupture and both recovered. The two deaths in the "late group" were due to leakage at the site of the rupture. This study suggests that even in patients diagnosed late as having rupture of the esophagus, primary repair can be implemented with reasonable success. Good mediastinal, pleural and gastric drainage, high levels of appropriate antibiotics, and provision of good nourishment are of paramount importance for the successful management of these desperately ill patients.

From the Joseph B. Whitehead Department of Surgery,
Thoracic and Cardiovascular Surgery Division,
Emory University School of Medicine, and
Grady Memorial Hospital, Atlanta, Georgia

SINCE SPONTANEOUS RUPTURE of the esophagus was first described by Boerhaave in 1724,[5] much has been written about it. The site of rupture has been consistently identified at the left posterior lateral aspect of the esophagus, just above the diaphragm.[3,8–10] The etiology has been attributed to an anatomic weakness in this area resulting from the reduced number and size of the longitudinal smooth muscle fibers, from the entrance of nerves and vessels into the wall, and from the lack of buttressing structures, such as liver and aorta, present on the right side. The precipitating event is usually forceful emesis,[5,8,10] and laboratory studies have demonstrated that increased intraluminal pressures from retching with a closed cricopharyngeous muscle could result in esophageal rupture.[11] The spectrum of presenting symptoms, the radiologic findings and the treatment, with all the attendant complications, have been throughly described.[1–4,7–10]

The mortality associated with spontaneous rupture of the esophagus still remains very high. In nonsurgically treated patients, it approaches 100% with 90% dying within 48 hours after rupture.[3,6,9] In the patients operated upon within 12 hours, the mortality is 22%,[3,9] but after 12 hours, it progressively increases to about 60%.[3]

Most investigators are in agreement that rupture of the esophagus should be treated by primary repair

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Address correspondence: Dr. P. N. Symbas, 69 Butler Street, S.E., Atlanta, Georgia 30303.

0003-4932-78-0600-0634-0085 © J. B. Lippincott Company

TABLE 1. *Case Reports*

Age, Sex Year of Admission	Interval from Onset of Symptoms to Admission	Initially Experienced Symptoms	Admission Diagnosis	Interval from Rupture to Correct Diagnosis	Interval from Rupture to Surgery	Operative Procedure	Postoperative Complications	Results and Hospital Stay
63 N/M (1971)	24 hours	Nausea, substernal pain, heart failure, angina	Myocardial infarction	26 hours	36 hours	T-tube esophageal drainage, pleural and mediastinal drainage, gastrostomy, jejunostomy	Sepsis, renal and respiratory failure	Deceased 16 days
81 W/F (1971)	12 hours	Epigastric pain and hematemesis	Upper gastrointestinal bleeding and acute myocardial infarction	40 hours	50 hours	Primary repair, pleural and mediastinal drainage	Respiratory failure and sepsis	Deceased 18 days
71 N/M (1971)	7 hours	Substernal pain and emesis	Esophageal rupture	9 hours	10 hours	Primary repair, pleural and mediastinal drainage	Pneumonia and superficial chest wound infection	Recovered 18 days
47 N/M (1972)	18 hours	Emesis and midscapular pain	Esophageal rupture	18 hours	23 hours	Primary repair, pleural and mediastinal drainage, gastrostomy, jejunostomy	Atelectasis and pneumonitis	Recovered 26 days
32 N/M (1972)	4 hours	Epigastric pain and retching	Esophageal rupture	6 hours	10 hours	Primary repair, pleural and mediastinal drainage, gastrostomy, jejunostomy	Small suture line leak and mediastinal abscess	Recovered 20 days
58 N/F (1974)	7 hours	Midscapular pain	Esophageal rupture	7 hours	20 hours	Primary repair, fundoplication, pleural and mediastinal drainage, gastrostomy, jejunostomy	None	Recovered 15 days
37 N/M (1975)	3 hours	Substernal and epigastric pain, dyspnea	Esophageal rupture	5 hours	8 hours	Primary repair, fundoplication, pleural and mediastinal drainage	None	Recovered 15 days
68 N/M (1975)	24 hours	Epigastric pain and hematemesis	Upper gastrointestinal bleeding, diabetes, renal tumor, arrhythmia hypertension	72 hours	76 hours	Primary repair, fundoplication, pleural and mediastinal drainage	Chest wound infection; twice upper gastrointestinal bleeding	Recovered 78 days
53 N/M (1977)	5 hours	Red blood per rectum, chest pain, vomiting	Spontaneous rupture of esophagus	5 hours	9 hours	Primary repair, fundoplication, pleural and mediastinal drainage	Continued gastrointestinal bleeding, gastric perforation, renal shutdown, cardiorespiratory arrest	Deceased 20 days

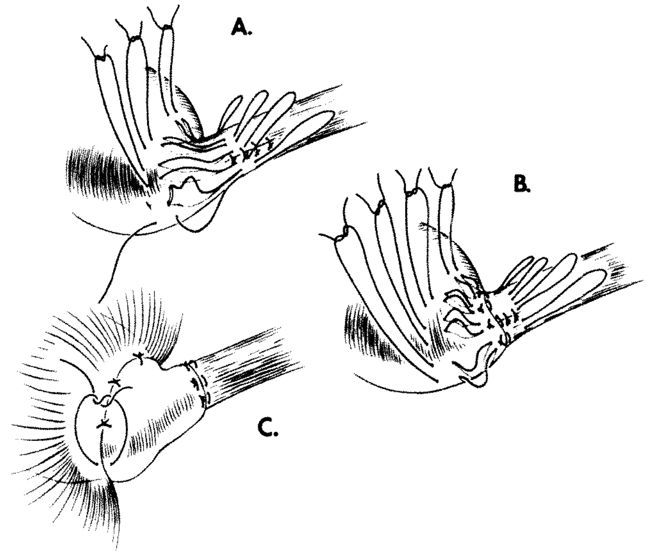


FIG. 1. (A) Esophageal rupture and placement of the first row of the fundoplication sutures. (B) First row of fundoplication sutures tied and placement of the second row of fundoplication sutures. (C) Fundoplication completed and the stomach is sutured to the diaphragm.

and drainage of the pleural and mediastinal spaces[1,2,6,8,10] when diagnosed early (less than 12 hours). On the other hand, the management of the patients with delayed diagnosis is quite controversial. Many reports claim that after 18–24 hours, only drainage procedures should be employed, as the esophageal wall is often too necrotic for a primary repair and the mediastinum is too contaminated to support healing.[1-3,7,8] Others have reported acceptable results with esophageal exclusion.[13] Still others advocate undertaking a primary repair, even in the face of delayed diagnosis and patient deterioration.[1,6,9,10]

The purpose of this communication is to review our last seven year experience with this clinical entity, managed with primary repair whenever the edges of the ruptured esophageal wall appeared to be able to support a suture line irrespective of elapsed time from rupture to surgery.

Clinical Material, Methods and Results

During the seven year period, 1971 to 1977, nine patients were diagnosed and treated for spontaneous rupture of the esophagus at Grady Memorial Hospital (Table 1). The time elapsed from the onset of symptoms to their arrival to the emergency room ranged from three to 24 hours (average 11.5). The initially experienced symptoms were retrosternal or midscapular chest pain with or without nausea or vomiting or epigastric pain with emesis or hematemesis. In four patients, the diagnosis of rupture was established and primary repair implemented early before the so-called critical 12 hour period of elapsed time. Three of these four survived. The fourth patient succumbed from continuous gastrointestinal bleeding manifested with bloody stools and hematemesis, hemoptysis, gastric perforation and renal failure. From the remaining five patients in whom surgical treatment was instituted late, more than 20 hours after the esophageal rupture, three were initially diagnosed as having acute myocardial infarction and/or upper gastrointestinal bleeding. This resulted in a great delay, 76, 50, and 36 hours after the rupture, respectively, in instituting the appropriate treatment for esophageal rupture. In one of the five patients in the "late group" who was operated upon 36 hours after rupture, T-tube esophageal drainage was used because the esophageal wound was thought to be too fragile and necrotic to be repaired primarily. He died 16 days later. Two other patients from this group underwent primary repair, resulting in one death 18 days later. The remaining two of the five "late group" patients underwent primary repair with fundoplication and both recovered. The primary repair was done in two layers after the margins of the ruptured mucosa were clearly identified and the necrotic and infected tissue surrounding the esophageal wound was adequately debrided. In the patients in whom fundoplication was also used

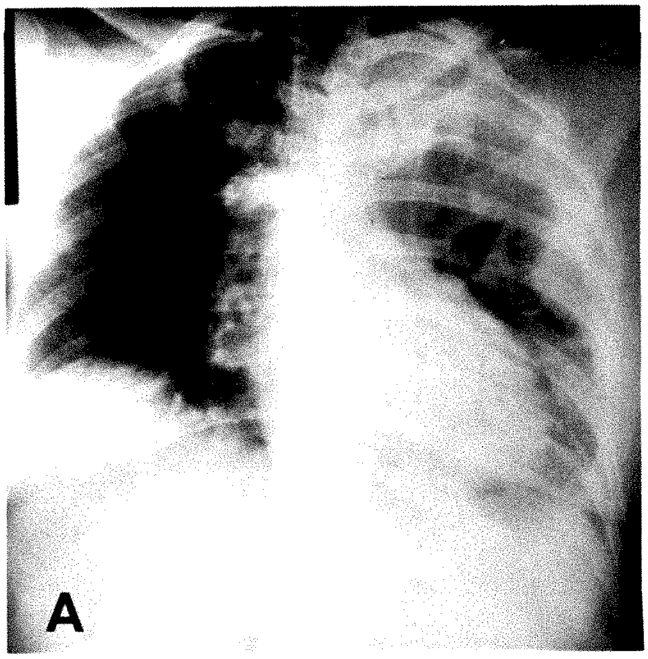


FIG. 2A. Roentgenographic studies of a 58-year-old woman who was admitted with midscapular pain of seven hours' duration. Admission supine chest roentgenogram. Note widened mediastinum, the pneumomediastinum and the diffuse radiodensity in the left pleural space.

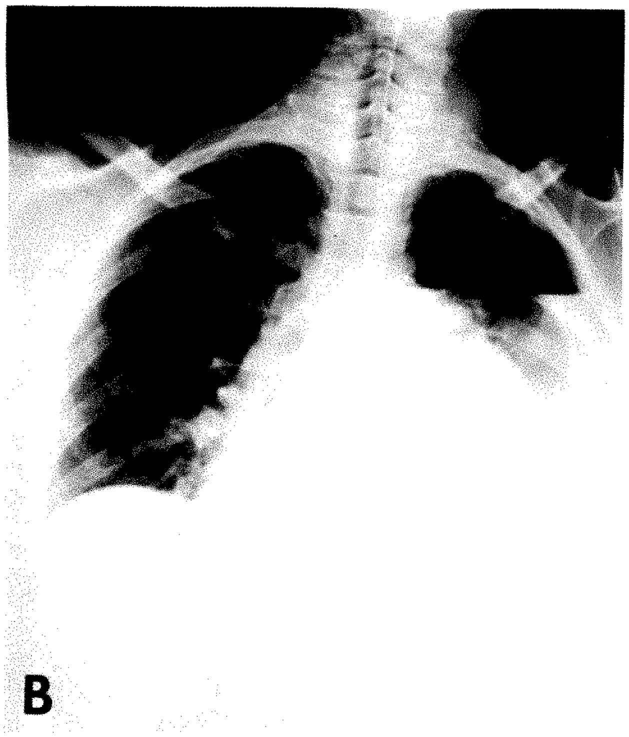


FIG. 2B. Same patient as in Figure 2A. Erect chest roentgenogram 16 hours later. Note the hydropneumothorax and the subcutaneous emphysema in the neck.

after the repair of the esophageal wound, the fundus of the stomach was brought over the suture line in 180° of the esophageal circumference as in Belsey-type fundoplication (Figs. 1 A and B). In three of the four patients who had this procedure, the fundoplicated segment of the esophagus and the segment of the stomach used for the fundoplication could not be brought below the diaphragm and thusly were left in the chest. In these three patients, in order to prevent future herniation of the stomach into the pleural space, the stomach was sutured to the diaphragm at the hiatus with interrupted sutures (Fig. 1 C). Two of the four patients with primary repair and fundoplication postoperatively developed empyema but the esophageal suture line remained intact.

All patients had operative and postoperative pleural and mediastinal drainage, preoperative, operative and postoperative intravenous antibiotics, and preoperative and postoperative gastric decompression. Four patients, three of whom survived, also had a gastrostomy and jejunostomy performed for drainage and alimentation. Of the three deaths, two were due to sepsis and renal and respiratory failure, both of whom belonged in the "late group" and the third death, which belonged in the "early group," was due to continuous gastrointestinal bleeding, gastric perforation, hemoptysis, hematemesis, and renal failure.

Comment

Our experience and that reported by other investigators emphasize that patients with spontaneous rupture of the esophagus treated early (less than 12 hours) with surgery have the best chance for survival. Accordingly, prompt and early diagnosis is the obvious cornerstone for successful management of these patients.

Esophageal rupture must be considered in the differential diagnosis of sudden onset of chest or epigastric pain, particularly when it occurs after heavy eating, drinking, or violent vomiting with or without hematemesis. When rupture of the esophagus is suspected, chest x-ray should be obtained to determine the presence or absence of mediastinal widening, pneumomediastinum, hydrothorax or hydropneumothorax (Figs. 2 A and B). When any of the above x-ray findings are present, the suspected diagnosis is affirmed but it should be definitely established by esophagography (Fig. 2 C).

Our current algorithm for the management of these patients is as follows. Once the diagnosis is established or preferably when it is strongly suspected, a nasogastric tube is inserted to empty the stomach and

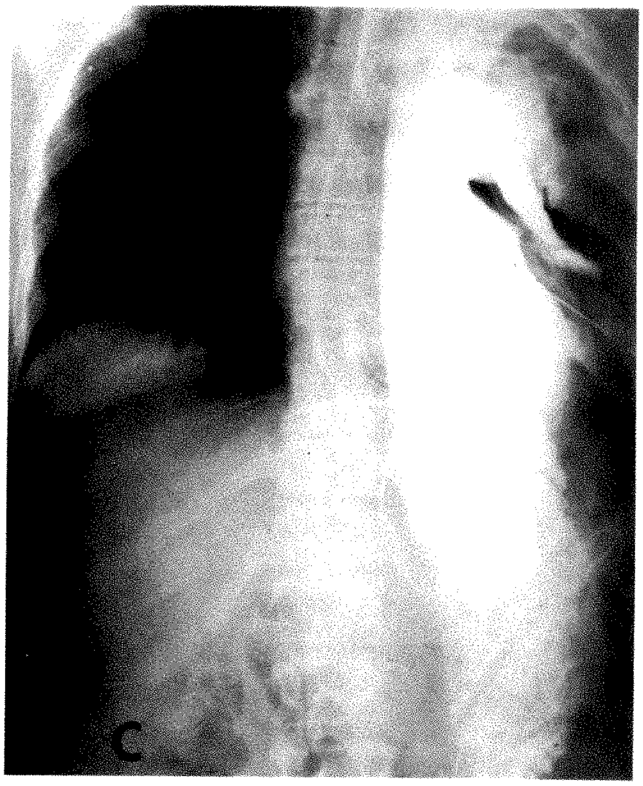
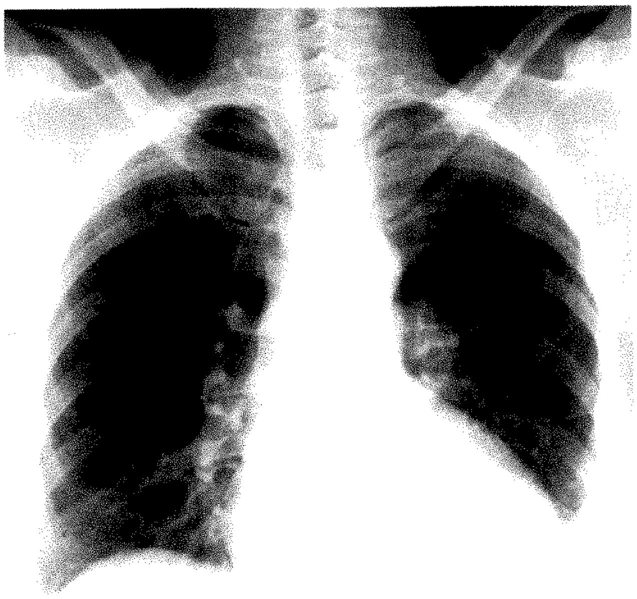


FIG. 2C. Same patient as in Figure 2A. Esophagogram 17 hours after admission. Note the extravasation of radiopaque material into the mediastinum and the left pleural space.



D

FIG. 2D. Same patient as in Figure 2A. Normal chest roentgenogram 15 days after primary repair with fundoplication of the 20-hour-old esophageal rupture.

prevent reflux with resultant mediastinal and pleural soiling. Broad spectrum antibiotics are administered intravenously to combat the infection resulting from the contamination of the mediastinum and pleural space. The patients are closely monitored and volume expanders are given as needed to replete the intravascular volume which frequently is lost into the mediastinum and pleural space. If hydrothorax or hydropneumothorax is present, immediate thoracostomy and drainage of the pleural space is performed.

After adequate preparation, the patient is operated upon as soon as possible. The operative procedure to be employed for the management of the esophageal defect is dependent upon the condition of the esophageal wall at the rupture site. If, after the necrotic and suppurative material has been adequately debrided and the edges of the ruptured mucosa clearly visualized, the esophageal wall appears viable and able to hold sutures, which in our experience and that of other investigators[6] has usually been the case, a primary repair of the wound is done. In the "late group," a fundoplication is also performed (Fig. 1). If, on the other hand, the wall appears to be fragile (although in the past, such a case was usually managed by closing the defect over a T-tube, which was brought out through the chest wall) now we might attempt to either close the defect with a fundic patch[12] or to ligate the cardia as a first stage and later, after healing has occurred, as a second stage, restore the continuity of the esophagus.[13]

Irrespective of the type of procedure used to handle the esophageal rupture, in all patients wide drainage of the mediastinum is done by incising the mediastinal pleura up to the aortic arch and drainage of the pleural space through two chest tubes is also done, as well as gastrostomy and feeding jejunostomy.

The postoperative management includes again close hemodynamic monitoring and maintenance of adequate circulatory blood volume with both crystalloids and colloids since these patients continue to lose a considerable amount of plasma into the mediastinum and pleural space, particularly during the first 24–48 postoperative hours. Good nourishment is maintained usually via jejunostomy or a small nasojejunal tube or transvenously to combat the catabolic state that frequently invests these patients. Also included are the intravenous administration of antibiotics, good pulmonary toilet, and frequent chest surveillance with x-rays for detection of any pulmonary, mediastinal or pleural changes. Loculated intrapleural pus pockets are promptly drained with a thoracostomy tube.

The use of fundoplication with primary repair of the ruptured area, particularly in the "late group" of patients, appears to enhance the healing of the suture line. None of our four patients (two in the "early" and two in the "late group") in whom this form of repair was utilized, had disrupture of the suture line, although two of them developed postoperative empyema which was managed with a thoracostomy tube. The functional significance, however, of leaving the fundoplicated segment of the esophagus in the chest in three of our four patients is not yet known and currently is being investigated in our laboratory.

References

1. Abbott, O. A., Mansour, K. A., Logan, W. D. et al.: Atraumatic So-called, Spontaneous Rupture of the Esophagus. J. Thorac. Cardiovasc. Surg., 59:67, 1970.
2. Bennett, D. J., Deveridge, R. J. and Wright, J. S.: Spontaneous Rupture of the Esophagus. Surgery, 68:766, 1970.
3. Blichert-Taft, M.: Spontaneous Oesophageal Rupture. Scand. J. Thorac. Cardiovasc. Surg., 5:111, 1971.
4. Bobo, W. O., Billups, W. A. and Hardy, J. D.: Boerhaaves Syndrome. Ann. Surg., 172:1034, 1970.
5. Boerhaave, H.: Atrocus, Nec Descriptiprius, Morbi Historia. Secundum Medicae Artis Leges Conscripta. Lugduni, Batavorum, Boutesteniana, 1974.
6. Bolooki, H., Anderson, I., Garcia-Rivera, C., et al.: Spontaneous Rupture of the Esophagus: Boerhaave's Syndrome. Ann. Surg., 174:319, 1971.
7. Callagan, J.: The Boerhaave Syndrome. Br. J. Surg., 59:41, 1972.
8. Froggatt, D. L. and Gunning, A. J.: Treatment of Esophageal Perforation. Thorax, 21:524, 1966.
9. Isaguirre, S. F. S., Haggerty, J. T. and Eckert, G.: Spontaneous Rupture of the Esophagus. Surgery, 67:607, 1970.

10. Keighley, M. R. B., Girdwood, R. W., Ionescu, M. I., et al.: Spontaneous Rupture of the Esophagus. Br. J. Surg., 59: 649, 1972.
11. Mackler, S. A.: Spontaneous Rupture of the Esophagus. Surg. Gynecol. Obstet., 95:345, 1952.
12. Thal, A. P. and Hatakuku, T.: Improved Operation for Esophageal Rupture. JAMA, 188:826, 1964.
13. Urschel, H. C., Razzuk, M. A., Wood, R. E., et al.: Improvement Management of Esophageal Perforation. Ann. Surg., 179:587, 1974.

DISCUSSION

DR. CHARLES E. DAVIS, JR. (Norfolk, Virginia): As you know, the history of this condition is truly fascinating, going back to the original decription by the great Boerhaave of Holland.

Last year my associates and I operated upon a 70-year-old woman with an emetogenic ruptured esophagus, who showed several unusual features. This patient was on the medical service for investigation of joint pain, and gagged following the ingestion of a Darvon® capsule. She immediately felt severe, burning pain in the lower chest and upper abdomen, and within a few hours exhibited severe peritonitis and sepsis.

X-rays showed free air in the mediastinum and the abdominal cavity. Contrast media revealed a leak from the lower esophagus, with the material extravasating widely into the mediastinum and also into the upper abdominal cavity. High abdominal exploration was carried out approximately 12 hours after rupture, as a joint thoraco-general surgical venture.

A profuse gastric content-barium peritonitis was obvious, the source being a clean-cut anterior linear laceration of the intra-abdominal esophagus. A gastrostomy was done, along with what was thought to be an adequate closure of the perforation, and wide drainage instituted.

Ten days later, the patient developed an esophageal fistula. Sepsis, malnutrition, electrolyte difficulties, anemia, bilateral pleural effusion and mental disorientation were among the many other problems encountered over a period of more than three months. Ultimately, the fistula healed, and she survived—we believe, due mainly to intravenous hyperalimentation, kindly supervised for us by Dr. John Baker of Norfolk.

Retrospectively, the addition of fundoplication would have greatly lessened the possibility of leakage, and it could have been so easily achieved, since the laceration was fundamentally intra-abdominal and anterior.

We agree with the authors that fundoplication is a valuable adjunctive measure where appropriate. Incidentally, in this era of catastrophic illness and astronomical costs, her hospital charges of approximately $36,000 for her 107 days in the hospital seem hardly worth mentioning.

She also now has a huge ventral hernia, which we will attack when her courage and ours have regenerated.

DR. JOHN L. SAWYERS (Nashville, Tennessee): I congratulate Dr. Symbas on his presentation which brings to us for review a clinical entity which is becoming of increasing importance. His suggestion to add fundoplication to reinforce the esophageal repair seems reasonable and effective.

(Slide) At the Vanderbilt University Medical Center in Nashville, we have noted an increasing incidence of esophageal perforations, as shown on this first slide. There has been a change in the etiology of the perforation. In previous years, most of the esophageal perforations were iatrogenic, occurring at the time of esophagoscopy or dilatation. Now we are seeing more perforations of the esohagus secondary to trauma and to the entity that Dr. Symbas has described, spontaneous perforation of the esophagus.

Eight patients with spontaneous esophageal perforation have been treated in the past ten years at our institution. The majority of these patients were admitted with an erroneous initial diagnosis as shown on this slide. Acute pancreatitis, myocardial infarction, perforated duodenal ulcer, and hiatal hernia were frequent admitting diagnoses.

All eight patients were treated by operation with an attempt to perform primary repair of the perforation and wide drainage of the mediastinum. Six of the eight patients survived.

We would emphasize, as Dr. Symbas has, the necessity for early treatment. This next slide shows the results of surgical treatment in relation to time in all of our patients who had esophageal perforation. When there was a delay in treatment beyond 24 hours, the mortality rate rose to 56%. Emergency operation is most applicable to patients who have an esophageal perforation secondary to spontaneous perforation, since this is even more of a lethal condition than traumatic esophageal perforation.

Since Dr. Symbas didn't show a slide of Boerhaave, I thought that you might be interested in seeing what he looked like. Boerhaave was the leading medical educator of his time and occupied three of the five chairs of the medical faculty in the University of Leyden in Holland. These chairs being theoretical and practical medicine, botany, and chemistry. (Slide)

The first reported case of spontaneous rupture of the esophagus was a detailed account of the short and fatal illness of Baren Von Wassenaer who was Grand Admiral of the fleet of Holland and who attempted vomiting after overeating. At the autopsy, which Boerhaave performed himself, extensive subcutaneous emphysema and pleural effusion were noted. Pleural effusion had the smell of duck flesh which the patient had eating the day before and was a clue which led Boerhaave to find the ruptured esophagus and publish his findings in a 70 page monograph, the title page is shown in this slide. For those of you who would like to have this interpreted, it reads, "History of Grievous Disease not Previously Described."

DR. GEORGE A. HIGGINS (Washington, D. C.): We have had a modest experience with this largely self-inflicted disease, as Dr. Sawyers has just pointed out to us.

One of the important problems is early recognition; and there is often a tendency to ascribe late diagnosis to the patient delay. However, one of our difficulties is that we often don't think of the diagnosis and therefore delay is very much iatrogenic.

(Slide) This illustrates one of our patients who emphasizes some of these points. This man came to the University Hospital first, where the diagnosis was not recognized, and somehow he arrived at our hospital and was found lying in front of the hospital at midnight. Later we estimated there was approximately 36 hours' delay. Incidentally he had previously had a transthoracic hiatal herniorraphy. At operation he had the typical 3 cm tear, left side, just above the hiatus, and we managed to salvage him with primary repair and supportive measures.

He was discharged on an alcohol rehabilitation program. One yer later he was found in the hallway of a rooming house by police and was again brought to the University Hospital, where the problem was recognized. At operation he had a 3 cm tear on the right side of the terminal esophagus, the only instance I have seen of both a left- and a right-sided spontaneous rupture of the esophagus.

I would add just one historical note to John Sawyers' discussion. If you're like I am, you have difficulty remembering whether Boerhaave was the patient or the physician who gets credit for first describing this condition. As you remember, his patient was a Baron van Wassenour, Grand Admiral of the fleet of Holland.

DR. DONALD L. PAULSON (Dalls, Texas): We have not had experience with fundoplication for perforations of the esophagus. Our experience with esophageal exclusion in continuity, as reported to you a few years ago, goes back now six years.

The concept of esophageal exclusion for chronic esophageal fistula is not new. However, esophageal exclusion, or occlusion, if you desire, in continuity, is our concept, and advocated by us in dealing with esophageal perforations, whatever the cause may be.

Say what we will about early diagnosis, most of these cases are late when we see them. The diagnosis is very tricky, and many of them are over 12 hours in duration, and the patient in a very serious condition, when we are seeing them. In the chronic cases of fistula the morbidity and mortality, as indicated this morning, are horrendous.

The procedure that we advocate is esophageal occlusion, or exclusion, in continuity, now using absorbable suture, a double strand of catgut, at the cardia, or esophagogastric junction, in addition to primary repair of the perforation. This is applicable particularly to the late cases; but in many of the early cases as well, to insure healing.

There is sufficient edema and swelling of the esophagus that by ligation we obtain an occlusion of the lower esophagus, and prevent gastroesophageal reflux of acid peptic juice, which we feel is responsible for reopening of the suture line. As the edema and the inflammation subside, the suture deteriorates. Usually within ten to 14 days the patency of the esophagus is re-established.

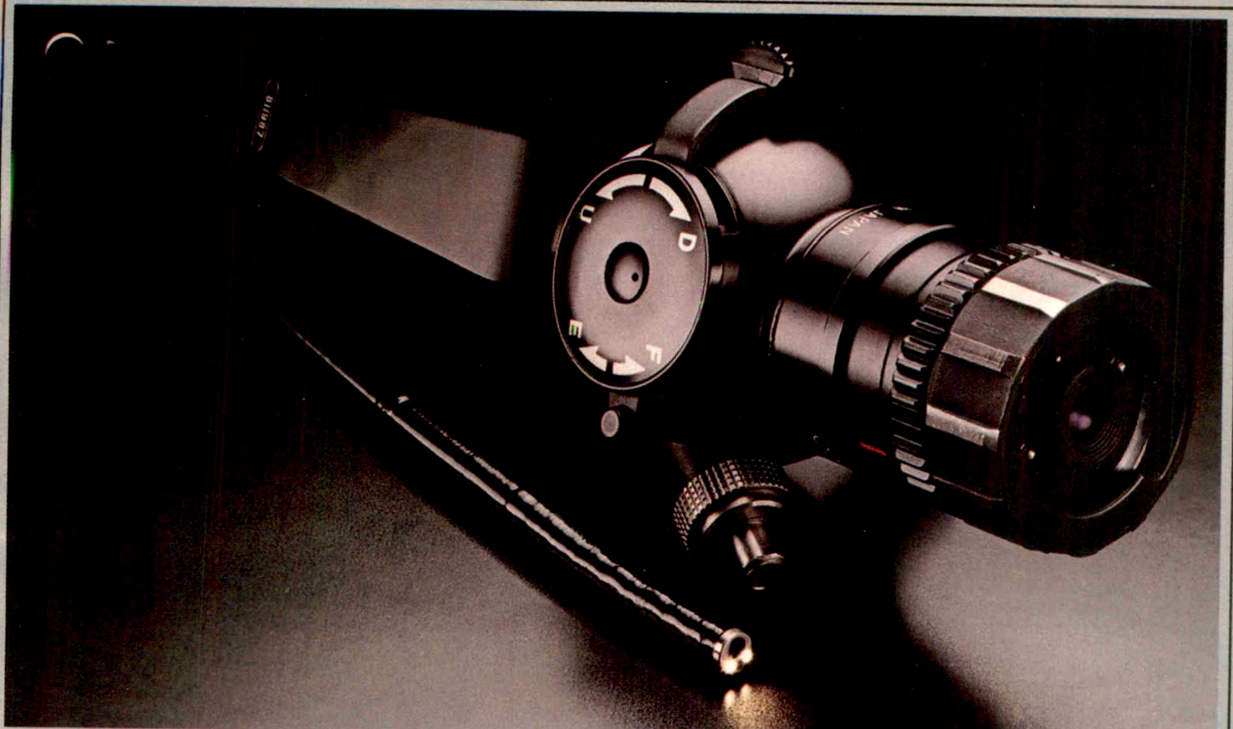
Since using this procedure, we have not had reopening of the suture line, and in the chronic cases, whatever the cause may be, the patients fistula has promptly healed. We originally advocated umbilical tape as the occlusive suture, but have now gone to the absorbable suture. However, in some of the long-standing, chronic fistulae, the use of umbilical tape may be justified, in order to obtain proper occlusion without strangulation of the esophagus, to give the fistula an opportunity to heal.

Dr. Panagiotis N. Symbas (Closing discussion): Dr. Sawyer's comments concerning the historical aspects of this syndrome are most appreciated since time did not allow me to pursue these facts.

As for Dr. Davis' interesting case, it is hard to comment retrospectively, but it seems to me that the fundoplication would have been of great value. We have used fundoplication in such a setting in a patient with traumatic perforation of the gastroesophageal junction with good results.

Dr. Paulson's comments concerning the utilization of the exclusion procedure for the management of spontaneous rupture of the esophagus is of particular importance. We have not used this procedure for spontaneous rupture of the esophagus but as I indicated in our presentation, when the occasion arises in very selective cases, we intend to use it. We have employed, however, the exclusion procedure in a modified form in a case with iatrogenic perforation of a stenosed and diffusely fibrosed esophagus. In this case, the esophagus was divided at its lower third and the proximal and distal stumps were sutured. The proximal esophageal pouch was drained with a tube passed transnasally. Despite its constant decompression, leakage into the mediastinum through the proximal esophageal stump occurred resulting in empyema and mediastinitis, which cleared after the appropriate drainage and the creation of a cervical esophagocutaneous fistula. Of course, since Dr. Paulson does not divide the esophagus as we did in our case, the risk of such a complication is less and, as he stated, one which he has not encountered.

WHEN YOU NEGOTIATE SMALL BRONCHI AT 500 MM YOU NEED THE BEST THERE IS.

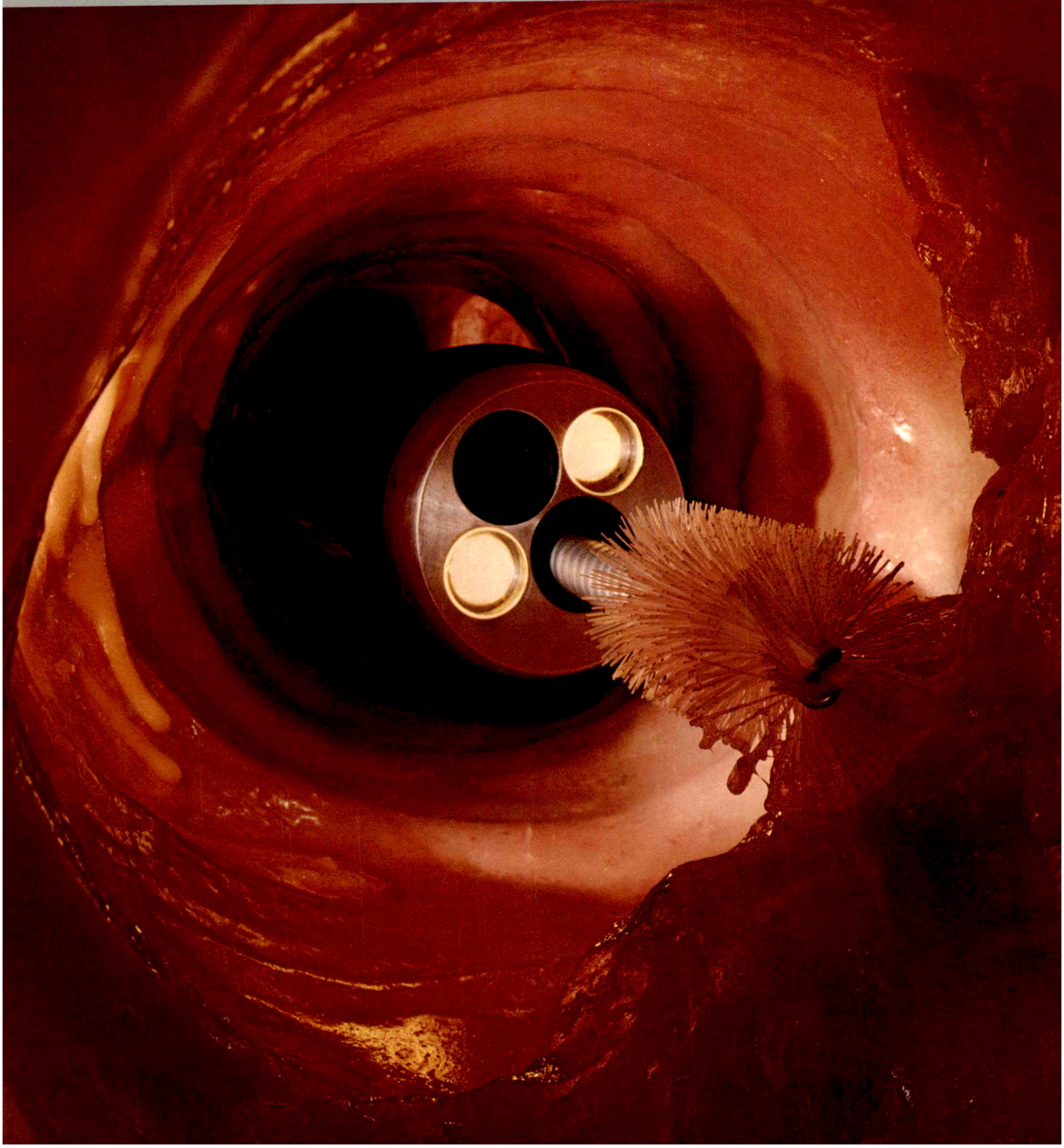


Nobody says that bronchoscopy is an easy procedure. That's why, when you're the one assuming the responsibility, it's important to know that you're using the world's most advanced bronchofiberscopes: Olympus.

Olympus bronchofiberscopes are built for smooth, comfortable insertion and maneuverability. They go where you want them to go. At the same time, their superior optics provide you with the highest degree of image clarity and brightness, while their wide range of accessories complements your skills precisely.

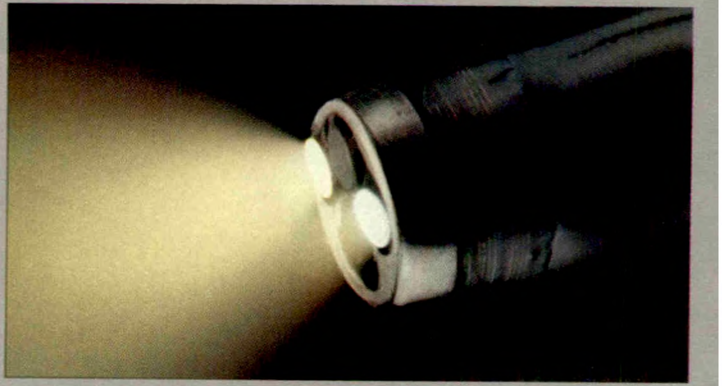
Olympus bronchofiberscopes. They're exactly what you need: the best.

OLYMPUS. PRECISION FOR DEMANDING PRO



BRONCHOFIBERSCOPES
EDURES.

The Olympus BF-B3 is the most versatile bronchofiberscope on the market today. Its slender construction and superb response allow for precise control and placement within the bronchial tree. The BF-B3 houses a 2-mm multipurpose channel for biopsy, cytology, suction and other procedures.



INTRODUCING A BRONCHOFIBERSCOPE YOU CAN GET A LOT MORE OUT OF.

The new large-channel BF-1T greatly expands your biopsy capabilities because its larger, 2.6-mm channel accommodates a greater array of cytology accessories and biopsy forceps. The larger channel also increases the instrument's suction power, while an added adapter provides precise regulation of suction with simple fingertip control, even during biopsy. The BF-1T is the bronchofiberscope that delivers.

Special-purpose instruments also available from the best-known line of precision bronchofiberscopes: BF-4C2 and BF-3C2 ultrathin bronchofiberscopes; BF-2T two-channel bronchofiberscope.

IF YOUR FIBERSCOPE EVER NEEDS SERVICE, YOU'LL BE GLAD IT'S AN OLYMPUS.

That's because of Olympus' nationwide network of service centers. They're not just local offices that forward a fiberscope that needs service to a central plant. Each regional service center is fully equipped to perform major and minor repairs and maintenance on all our fiberscopes and accessories. Which means that if your scope has to come in for service, you have less time to wait for it to come back—or, in an emergency, less time to wait for a loan instrument. It's a service organization that no other fiberscope manufacturer can even come close to—in size or efficiency.

Unretouched photo taken through an Olympus fiberscope.

The only nationwide network of fully equipped fiberscope service centers:
Baltimore,
Chicago,
Houston,
Jacksonville,
Los Angeles,
New York.

OLYMPUS

SUPERIORITY YOU CAN SEE.

Olympus Corporation of America, Medical Instrument Division,
4 Nevada Drive, New Hyde Park, New York 11040, (516) 488-3880

I'd like to look into Olympus. B AS6

Send me further information on the following Olympus fiberscopes: ____________________

☐ Have your representative call me to arrange an appointment.

Name ____________________
Position ____________________
Institution ____________________
Address ____________________
City __________ State __________ Zip __________
Telephone (   ) ____________________

Inferior Mesenteric Artery Stump Pressure:

A Reliable Index for Safe IMA Ligation During Abdominal Aortic Aneurysmectomy

CALVIN B. ERNST, M.D., PATRICK F. HAGIHARA, M.D., MICHAEL E. DAUGHERTY, M.D.,
WARD O. GRIFFEN, JR., M.D.

From the Department of Surgery, Vascular Surgery Service, University of Kentucky Medical Center, Lexington, Kentucky

Fifty-two patients undergoing nonemergent abdominal aortic aneurysmectomy were prospectively studied to determine when the inferior mesenteric artery (IMA) could be ligated without subsequent development of ischemic colitis. Cannulation of the severed distal IMA for blood pressure measurement (IMA stump pressure) before and after aortic reconstruction was attempted in all and possible in 39 individuals. In 13 the IMA was thrombosed precluding pressure measurement. Prereconstruction and postreconstruction mean IMA stump and systemic arterial blood pressure measurements were computed and mean IMA/systemic pressure ratios were calculated. All patients underwent postoperative colonoscopy. One patient developed postoperative ischemic colitis. Her postreconstruction ratio was 0.37 and her postreconstruction mean IMA blood pressure was 33 mmHg, the only individual with a ratio and pressure less than 0.40 and 40 mmHg, respectively. Internal iliac arterial pulsations could not be restored in two patients. Although postresection indices were less than preresection indices in both, postresection indices were greater than 0.40 and 40 mmHg. In this study, if the IMA was thrombosed or if postresection pressures and ratios measured greater than 40 mmHg and 0.40 respectively, ischemic colitis did not develop following abdominal aortic aneurysmectomy. This simple test may prove useful in identifying patients at risk for developing postoperative ischemic colitis or if IMA revascularization is required.

ISCHEMIC COLITIS following abdominal aortic aneurysmectomy results in significant morbidity and mortality[1,7-10] The sporadic occurrence of this complication makes etiology difficult to clearly establish. While ligation of the inferior mesenteric artery (IMA) is common to development of most reported instances of ischemic colitis following operations on the abdominal aorta, other causative factors are also cited. These include improper IMA ligation, failure to restore IMA or internal iliac arterial blood flow, severe operative hypotension and hypoperfusion, inadequate existing or potential collateral communications between the inferior and superior mesenteric arterial systems, and manipulative trauma to the colon.[7-10]

Early detection of ischemic colitis is mandatory for decreasing mortality and morbidity rates from this complication of aortic reconstruction. This may be accomplished in the postoperative period by routine use of sigmoidoscopy or colonoscopy.[1,3,10] Prediction of this complication by an objective test should aid in prevention. In addition, an objective means of determining when the IMA may be safely ligated would be helpful.

Giving cause for thoughtful concern in a previous study was the unreliability of palpating an inferior mesenteric arterial pulse following aortic reconstruction and prediction of subsequent development of ischemic colitis.[3] Accurate estimation of colonic viability prior to abdominal closure proved impossible. To obtain objective data from which might be determined when the inferior mesenteric artery could be ligated without subsequent development of ischemic colitis, 52 patients undergoing nonemergent abdominal aortic aneurysmectomy were studied prospectively and form the basis of this report. All underwent postoperative colonoscopy. An attempt was made to measure prereconstruction and postreconstruction blood pressure in the distal inferior mesenteric artery after transection (IMA stump pressure) in all patients.

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Reprint requests: Calvin B. Ernst, M.D., Department of Surgery, Vascular Surgery Service, University of Kentucky Medical Center, Lexington, Kentucky 40506.

Supported by the University of Kentucky Vascular Surgery Research and Education Fund.

0003-4932-78-0600-0641-0075 © J. B. Lippincott Company

TABLE 1. *Age and Sex Distribution*

Age	Men	Women
40–49	1	—
50–59	8	5
60–69	16	4
70–79	13	3
80–89	2	—
Total	40	12

Clinical Material and Methods

Patient Population

Of the 52 patients studied, 40 were male and 12 female. Their average age was 66 years, ranging from 49 to 85 years (Table 1). Onset of severe back pain during evaluation required urgent operation in two individuals. Thirteen other patients experienced mild abdominal or back pain or embolic phenomena from the aneurysm, but did not require urgent aneurysmectomy. These 15 patients were considered to have symptomatic abdominal aortic aneurysms. In the remaining 37 patients, the abdominal aortic aneurysm was asymptomatic. No emergency operations were performed and no ruptured aneurysms were encountered.

Seventy-seven per cent of individuals had clinically significant evidence of diffuse vascular disease including previous myocardial infarction, angina, stroke, intermittent claudication, arterial hypertension, or other significant degenerative processes such as chronic obstructive pulmonary disease and diabetes mellitus.

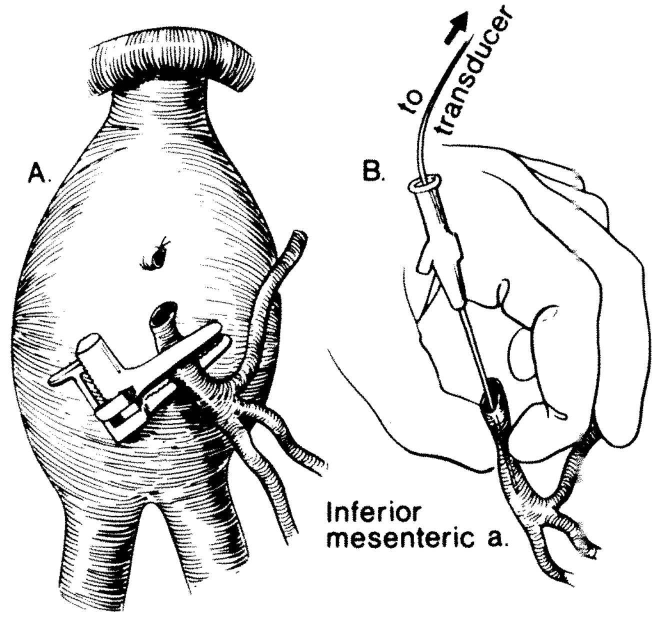


FIG. 1. Inferior mesenteric arterial stump pressure measurement. (B) Cannula secured between thumb and forefinger during measurement. (A) Vascular clamp on IMA during aortic reconstruction, before postreconstruction measurements.

Technique

Through radial artery cannulae, systemic arterial blood pressure was measured in all patients during operation. After opening the retroperitoneum, the inferior mesenteric artery (IMA) was dissected over a distance of 3–5 cm to the IMA-aortic junction. After ligating the IMA at the aorta, it was divided and the distal end cannulated with an 18 gauge two inch long disposable Teflon catheter (Angiocath®) (Fig. 1). After thoroughly flushing the connector tubing with heparin–saline solution and attaching it to the catheter, IMA stump pressure was measured using a Statham pressure transducer (Model P23 Series). Immediately following IMA blood pressure measurement, systemic arterial blood pressure was obtained and both pressure measurements recorded. After removing the IMA catheter, a vascular clamp was placed on the divided distal IMA (Fig. 1).

Standard aortic aneurysmectomy, leaving the posterior aneurysm wall *in situ*, was performed in all instances. All repairs required bifurcation prostheses except two in which tube grafts were employed (Table 2). In eight individuals, both distal anastomoses were to be femoral arteries. In two others, one limb of the prosthesis was anastomosed to the femoral artery and the other limb to the iliac artery. In the remaining 40 reconstructions, distal anastomoses were to the iliac vessels bilaterally (Table 2). Three patients required concomitant visceral arterial reconstruction, two renal revascularizations, and one superior mesenteric arterial revascularization.

Following reconstruction and restoration of blood flow to the legs, IMA stump blood pressure and systemic arterial blood pressure measurements were repeated. The inferior mesenteric artery was ligated in all patients. Inferior mesenteric arterial reconstruction was not performed. When identified, the meandering mesenteric artery was preserved in all patients. Assessment of internal iliac arterial pulsation by palpation was made in all patients.

Aortography

Preoperative aortographic studies were performed in 36 of the 52 patients. Arteriograms were scrutinized and inferior mesenteric and internal iliac arterial patencies were recorded. When possible, superior mesenteric arterial patencies were noted. Inferior mesenteric artery opacification by a superior mesenteric collateral (meandering mesenteric artery) was particularly noted.

TABLE 2. *Methods of Aortic Reconstruction**

Aorto-aortic	2
Aorto-iliac-femoral	2
Aorto-bi-femoral	8
Aorto-bi-iliac	40

* Visceral revascularization in three.

Colonoscopy

Postoperative colonoscopy was performed in all patients within four days of aortic aneurysmectomy. The average time interval was 2.7 days. Bowel preparation was accomplished by preoperative mechanical cleansing with saline enemas. Oral antibiotics were not used. With use of the 105 cm Olympus colonoscope, all studies were performed by a single examiner (P.F.H.). The colonoscope was passed an average distance of 39 cm from the anal verge. If ischemic colitis was identified, the study was terminated. Passage of the colonoscope beyond the involved bowel segment was avoided.

Results

IMA stump blood pressure measurements were obtained in 39 patients. In the remaining 13, a thrombosed IMA precluded pressure measurement. Prereconstruction and postreconstruction mean IMA stump and systemic arterial blood pressure measurements were computed and mean IMA/systemic pressure ratios were calculated.

Preresection pressure ratios averaged 0.71 (range: 0.31–0.99). Postresection pressure ratios averaged 0.71 (range: 0.37–0.97) (Fig. 2). Prereconstruction mean IMA blood pressures averaged 70 mmHg, and postreconstruction mean IMA blood pressures averaged 67 mmHg (Fig. 3). In 21 individuals (54%) postresection IMA/systemic ratios were greater than preresection ratios, and mean IMA stump blood pressures after reconstruction were greater than mean IMA stump blood pressures before reconstruction. The average decrease in mean IMA blood pressure among those patients whose mean IMA blood pressures fell after reconstruction was 21 mmHg (range: 3–47 mmHg).

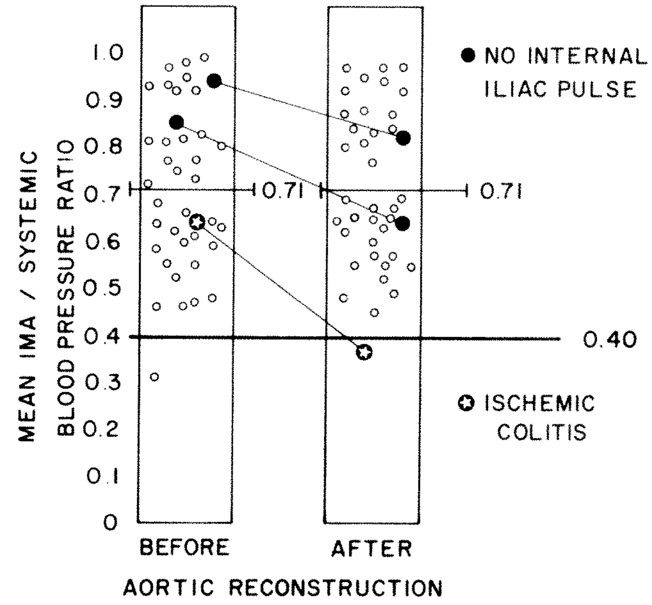


FIG. 2. Graphic comparison of mean IMA/systemic blood pressure ratios before and after aortic reconstruction in 39 patients.

One patient developed ischemic colitis postoperatively. Her postreconstruction IMA/systemic blood pressure ratio was 0.37, the only individual with such a ratio less than 0.40 (Fig. 2). In addition, her mean IMA stump blood pressure measured 33 mmHg following aortic reconstruction, the only patient with such a pressure less than 40 mmHg (Fig. 3). IMA/systemic blood pressure ratio decreased from 0.64 before reconstruction to 0.37 after reconstruction, while mean IMA blood pressure fell from 80 mmHg before reconstruction to 33 mmHg after reconstruction. Distal arterial reconstruction was to the common iliac arteries bilaterally and both internal iliac arterial pulses were felt after restoration of blood flow. Mild ischemic colitis was identified on the second postoperative day. Almost complete resolution was noted eight days following operation and recovery proceeded uneventfully.

At least one internal iliac arterial pulse was palpable following restoration of blood flow in all patients except two (Figs. 2 and 3). In both, internal iliac arterial flow was precluded by the type of distal arterial reconstruction. One patient required end-to-end recon-

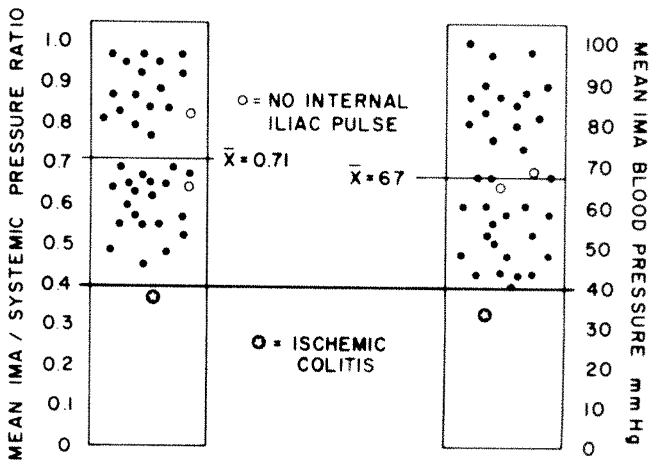


FIG. 3. Mean IMA/systemic blood pressure ratios and mean IMA blood pressure measurements following aortic reconstruction in 39 patients. Ischemic colitis occurred when indices fell below 0.40 and 40 mmHg.

struction to external iliac arteries and in the other extensive atherosclerosis prevented retrograde flow from the femoral arteries into the internal iliac arteries. Although postreconstruction IMA/systemic blood pressure ratios were less than prereconstruction ratios in both, in neither patient was the ratio less than 0.40 following reconstruction (Fig. 2). Mean IMA stump blood pressures decreased in both individuals following repair (20 and 22 mmHg), but remained greater than 40 mmHg (Fig. 3). Neither patient developed ischemic colitis.

Ischemic colitis did not develop among the 13 patients noted to have thrombosed inferior mesenteric arteries at operation. Twelve of these 13 underwent preoperative aortography. In seven of these 12 the meandering mesenteric artery was identified on arteriograms.

The meandering mesenteric artery was noted on 12 of 36 arteriographic studies. Ischemic colitis did not develop in any patient in whom the meandering mesenteric artery was identified and preserved. Internal iliac arterial opacification was identified in 33 of the 36 arteriographic studies. In 11 of the 36 arteriographic studies, the IMA was noted.

Discussion

Ischemic colitis incidence following abdominal aortic reconstruction varies from 1.5–10%.[3,7,9] The reported 40% mortality rate from this complication suggests that delay in diagnosis may preclude effective treatment.[7] This is especially true for transmural ischemia which leads to death in 70% of cases. Refinements in operative techniques, improved patient support capabilities, and sophisticated monitoring methods have contributed to progressive declines in mortality and morbidity rates for abdominal aortic aneurysmectomy. Prediction of development of ischemic colitis should further lower mortality and morbidity for abdominal aortic reconstruction, since effective therapy may be employed early during development of such a complication.[3] In addition, prediction may prevent this complication by identifying which patients require reconstruction of the inferior mesenteric artery.

Why this complication occurs sporadically is unknown but differing etiologies no doubt account for some of this variance. Previous excellent reviews have identified several factors which affect development of ischemic colitis following abdominal aortic aneurysmectomy (7–10). Prediction of development of ischemic colitis is challenging under such circumstances.

Except for the report of Hobson and coworkers, no attempts have been made to obtain objective data from which prediction of development of ischemic colitis may be made.[6] These investigators concluded that presence of audible doppler flow over the base of the large bowel mesentery and serosal surface of the left colon may correlate with viability of the bowel. Routine postoperative colonoscopy to detect ischemic colitis, however, was not employed in their study. Clinically overt ischemic colitis did not develop.

Measurement of IMA stump blood pressure may offer advantages over hearing doppler flow signals because flow may be present even though perfusion pressure, less than the critical closing pressure of the nutrient bed (mucosal) vessels, is low. Critical closing pressure is approximately 40 mmHg.[4] A false sense of security may accompany hearing doppler flow signals if perfusion pressure is less than 40 mmHg. Complete cessation of flow, however, appears to be a discriminating end point with doppler evaluation.[6] Measurement of blood pressure in the distal segment of the transected inferior mesenteric artery was easily accomplished in this study. Such measurements added no more than 10 minutes to each operative procedure.

One patient in the present study developed ischemic colitis following abdominal aortic aneurysmectomy. Internal iliac pulses were felt following restoration of blood flow, undue trauma to the sigmoid colon was not apparent during operation, and systemic hypotension and hypoperfusion did not occur. The patent inferior mesenteric artery was correctly ligated, preserving the ascending and descending arcades of this vessel. Mean IMA stump blood pressure following aortic reconstruction, however, measured only 33 mmHg and the IMA/systemic blood pressure ratio was 0.37. This was the only patient in this study with a mean IMA blood pressure less than 40 mmHg or an IMA/systemic ratio less than 0.40 following reconstruction (Fig. 3). In addition, the 47 mmHg drop in mean IMA pressure following repair in this individual was the greatest decline identified.

Internal iliac arterial blood flow could not be restored in two individuals. Although postresection IMA/systemic blood pressure ratios and mean IMA stump blood pressure values were less than preresection ratios and pressures in both, these postresection indices were greater than 0.40 and 40 mmHg, respectively (Figs. 2 and 3). Neither patient developed postoperative ischemic colitis. IMA stump blood pressure data verified adequacy of collateral circulation in these two patients and predicted that the IMA could be safely ligated even though internal iliac arterial pulsation could not be restored.

Preoperative aortography may prove useful in identifying patients at risk for developing ischemic colitis.[2,3,7] The meandering mesenteric artery was noted in 36% of patients. Ischemic colitis did not develop among patients having this collateral documented. Preoperative recognition of the meandering mesenteric artery aids in avoidance of injury to this vital vessel. No correlation, however, between preoperative hypogastric arterial opacification and colon ischemia could be identified.

When to restore mesenteric arterial flow by reimplantation of the IMA or an interposition graft from the prosthesis to the IMA cannot be conclusively determined from this study. Other investigators have attempted to answer this question on clinical and empirical grounds.[5-7] Since ischemic colitis is an unusual complication, acquisition of objective data by a prospective randomized study would seem to be beyond practicality. Nonetheless, indirect evidence from this study would justify revascularization of the IMA if postresection mean IMA blood pressure measures less than 40 mmHg or an IMA/systemic ratio less than 0.40 is identified.

In this prospective study, if the IMA was thrombosed or if postresection mean IMA blood pressure or IMA/systemic pressure ratios measured greater than 40 mmHg and 0.40, respectively, ischemic colitis did not develop following aortic aneurysmectomy. Under such circumstances, the IMA may be safely ligated. Pressures less than these values forewarn possible development of ischemic colitis and the need for prompt diagnosis. Therapy may then be instituted before advanced clinical manifestations preclude effective management. Adoption of IMA stump blood pressure measurements correlated with postoperative colonoscopy findings may prove useful in identifying patients at risk for developing ischemic colitis and when IMA revascularization is required.

References

1. Bernatz, P. E.: Necrosis of the Colon Following Resection for Abdominal aortic Aneurysms. Arch. Surg., 81:373, 1960.
2. Brewster, D. C., Retana, A., Waltman, A. C. and Darling, R. C.: Angiography in the Management of Aneurysms of the Abdominal Aorta. N. Engl. J. Med., 292:822, 1975.
3. Ernst, C. B., Hagihara, P. F., Daugherty, M. E., et al.: Ischemic Colitis Incidence Following Abdominal Aortic Reconstruction: A Prospective Study. Surgery, 80:417, 1976.
4. Folkow, B. and Neil, E.: Gastrointestinal and Liver Circulations. *In* Circulation, New York, Oxford University Press, 1971.
5. Hardy, J. D. and Timmis, H. H.: Abdominal Aortic Aneurysms: Special Problems. Ann. Surg., 173:945, 1971.
6. Hobson, R. W., II, Wright, C. B., Rich, N. M. and Collins, G. J., Jr.: Assessment of Colonic Ischemia During Aortic Surgery by Doppler Ultrasound. J. Surg. Res., 20:231, 1976.
7. Johnson, W. C. and Nabseth, D. C.: Visceral Infarction Following Aortic Surgery. Ann. Surg., 180:312, 1974.
8. Ottinger, L. W., Darling, R. C., Nathan, M. J. and Linton, R. R.: Left Colon Ischemia Complicating Aorto-Iliac Reconstruction. Arch. Surg., 105:841, 1972.
9. Smith, R. F. and Szilagyi, D. E.: Ischemia of the Colon as a Complication in the Surgery of the Abdominal Aorta. Arch. Surg., 80:806, 1960.
10. Young, J. R., Humphries, A. W., deWolfe, V. G. and LeFevre, F. A.: Complications of Abdominal Aortic Surgery. Arch. Surg., 86:51, 1963.

DISCUSSION

DR. FRANK E. SCHMIDT (New Orleans, Louisiana): We have taken a more pragmatic approach to the inferior mesenteric artery in resecting abdominal aortic aneurysms. When we have found the artery to be patent, with backbleeding, we have routinely anastomosed it, end to side, to the body of the Dacron® graft.

To facilitate this, we have used the technique described by Drs. Crawford and Morris, excising a button of aortic tissue around the origin of the artery, which makes the anastomosis much easier. We have found that this anastomosis adds only ten to 15 minutes to the length of the operation, and we have identified no complications related to this anastomosis. We have had no cases of ischemic colitis during the five years we have routinely performed it.

DR. WILLIAM H. EDWARDS (Nashville, Tennessee): Fortunately, ischemic colitis is seen infrequently. As he has pointed out, when it does occur, it can be catastrophic. We have not encountered this problem in the resection of the routine abdominal aneurysm. We have, however, seen it in those patients with ruptured abdominal aneurysms.

We routinely employ aortography prior to surgery in the patient with the nonemergent abdominal aneurysm, and we feel that with the aortogram we make a determination as to the patency or occlusion of the inferior mesenteric artery, and then decide whether we are going to anastomose it to the Dacron interposed graft.

(Slide) In this aortogram in a patient with a large inferior mesenteric artery, with several large branches, we elected to implant this into the Dacron prosthesis. We also attempt to utilize the button technique, but have found that in so many of these patients the atherosclerotic disease which is present at the origin of the vessel requires an endarterectomy, and we very frequently end up with a very small vessel that we directly anastomose to the Dacron.

(Slide) Another aortogram, not in a patient with an aneurysm, but in a patient with occlusive disease, shows a very tiny terminal aorta with a large inferior mesenteric artery. This is the inferior mesenteric, (indicating) and there is a tight stenosis present at the origin of that vessel. We elected to anastomose this to the Dacron.

Again, I would like to congratulate Dr. Ernst on his presentation and the work. We have had occasion in the past year to reimplant the inferior mesenteric artery on three occasions, and, I think, would continue to do this in those patients in which we feel we have a large vessel which is still patent.

DR. GARLAND D. PERDUE (Atlanta, Georgia): I don't think aortography is routinely required in all patients undergoing aneurysmectomy, but, rather, for specific indications. Because of the disastrous nature of ischemic colitis, one of the factors that one must be alert to, if one does not employ a routine aortography, is the existence of a vital IMA. I think it may be recognized by an unusually large size, by poor backbleeding of the patent artery, and by the known absence of otherwise normal, or expected, collateral pathways.

In these circumstances, we have also chosen to reimplant the IMA by the Crawford technique. Transmural endarterectomy is occasionally desirable. We find that in the last 500 aortic reconstructions we have implanted it 2% of the time, and have not observed ischemic colitis in this group of patients, who were done electively. It is most likely to occur in the patient who has prolonged hypotension, or recurrent hypoperfusion, usually in association with rupture of an aortic aneurysm.

I appreciate the precision of the suggestion, though, because I believe that it will enable us to determine more accurately which patients do require IMA reimplantation.

DR. GEORGE C. MORRIS, JR. (Houston, Texas): In a period of 25 years, some changes in technique have evolved, and I think some of these have not been emphasized in the literature: I would like to review some of these.

Firstly, we believe that retroperitoneal dissection should be minimal or nil, and in this connection, generally I clamp the iliac arteries before the aorta, without dissection, usually clamping the veins with the vessels. This precludes "trash-foot" or microembolization.

If a giant meandering artery of Drummond is found, you'll recognize it, and you don't need preoperative aortography to do this. If it's found, not only had you better put the inferior mesenteric artery back, but usually you'd better put something back to the superior mesenteric or the celiac axis, because the presence of a meandering artery signifies occlusion of the celiac and superior mesenteric arteries.

No resection of the aneurysm sac is performed. With this technique, we're able to utilize a tube graft, without using a bifurcation graft, in well over 80% of cases.

Following this principle, I have had one case of ischemic left colon in 25 years, and this particular case was due specifically to a dissecting hematoma in the mesentery of the sigmoid.

DR. CALVIN B. ERNST (Closing discussion): Dr. Morris, it would be very presumptuous of me to try to advise you how to perform aneurysmectomies with your 25 years of experience. Clearly, patients and surgeons alike have benefited from the Houston experience and teaching. As noted, only in two individuals were we able to use tube grafts. Ninety-six per cent of our patients had extensive aneurysmal disease requiring bifurcation prostheses for reconstruction. Limited dissections under such circumstances would not be satisfactory.

We do not routinely reimplant the inferior mesenteric artery. None were reimplanted in this series. By this study we hoped to gain objective data from which might be determined when the IMA could be ligated or when it should be reimplanted. Since we did not reimplant the IMA, I cannot say if doing so would prevent ischemic colitis. Since ischemic colitis is an unusual complication, acquisition of objective data by a prospective randomized study would seem to be beyond practicality.

Dr. Perdue, we feel that aortography is very helpful in identifying patients at risk for developing ischemic colitis. A major collateral channel supplying the IMA circulation when the IMA is occluded at the aorta is meandering mesenteric artery. When the meandering mesenteric is identified on serial radiographs as reconstituting IMA flow, the risk of developing colon ischemia is negligible, provided that this vital channel is recognized and preserved during operation. Being forewarned by aortography is forearmed in this setting.

Finally, we must continue to attempt to identify patients at risk for developing ischemic colitis to reduce the morbidity and mortality for elective abdominal aortic aneurysmectomy. If such ischemia is predicted or identified prior to clinical manifestations, it is possible that continued evaluation and treatment may be instituted before advanced clinical manifestations preclude effective therapy. To our previously published indications for postoperative colonoscopy we add documentation of a postreconstruction IMA stump pressure of less than 40 mmHg or finding a IMA/systemic ratio less than 0.40.

Extra-anatomic Bypass of the Abdominal Aorta:

Management of Postoperative Thrombosis

ROBERT W. OBLATH, M.D., RICHARD M. GREEN, M.D., JAMES A. DEWEESE, M.D., CHARLES G. ROB, M.D.

From the University of Rochester Medical Center, Department of Surgery, Rochester, New York

Extra-anatomic bypass of the abdominal aorta was performed in 25 patients too ill to undergo abdominal operation (Group I) and in 22 patients with graft sepsis or hemorrhage (Group II). The graft patency rate determined by life table analysis in Group I patients was 83.5% at one year and 60% at two years. The graft patency rate for Group II patients of 47% at one year was significantly lower than the patency rate for Group I patients ($p < .01$). Thrombectomy was attempted in 11 of the 18 grafts that occluded postoperatively. Patency was re-established by this method in nine grafts (82%), failures resulted in amputation. Recurrent occlusion of three thrombectomized grafts was treated by multiple thrombectomies with cumulative patencies up to 44.5 months. Thrombectomy was not attempted in seven occluded grafts. Two graft occlusions resulted in amputation of extremities. Contralateral axillofemoral grafts were performed in three of the patients, ipsilateral axillofemoral graft in one patient, and aortobifemoral graft in one patient. Thrombectomy is the treatment of choice for occluded extra-anatomic bypass grafts. It can be performed easily under local anesthesia. If unsuccessful, contralateral axillofemoral or femoro-femoral grafts are indicated to re-establish blood flow.

EXTRA-ANATOMIC BYPASS of the abdominal aorta is a recognized procedure for revascularizing the lower extremities of the poor risk patient with aorto-iliac occlusive disease, and for the patient with technical complications involving the abdominal aorta such as hemorrhage from the proximal aortic anastomosis, aorto-enteric fistulae, and prosthetic graft sepsis.[1,11,20] Graft thrombosis rates as high as 28% in the first six postoperative months have, however, limited the elective use of these grafts.[10] The etiology of extra-anatomic graft thrombosis has been attributed to external graft compression, the absence of healing, the absence of supporting fibrous capsule about the graft, progression of atherosclerotic disease with limitation of outflow,[13,19] and intimal hyperplasia at the proximal anastomosis.[5,16] Graft thrombectomy under local anesthesia has been suggested by both LoGerfo[10] and Mannick[12] as a method of prolonging long-term patency.

The records of 47 patients with 71 extra-anatomic bypasses were reviewed. The results of early thrombectomy for thrombosis of extra-anatomic bypasses were analyzed and compared with other methods of management.

Materials and Methods

There were 71 extra-anatomic bypasses of the aorto-iliac system with 10 mm woven or knitted Dacron® grafts performed on 47 patients between April 1970 and June 1976 by the resident and attending staffs of Strong Memorial Hospital. Eight femoro-femoral, four axillobifemoral, and 59 axillofemoral grafts were inserted.

Indications for operation were aorto-iliac occlusive disease in which abdominal operation was contraindicated (Group I: 25 patients, 34 extremities) or for sepsis and/or hemorrhage from the proximal abdominal aorta (Group II: 22 patients, 37 extremities). Group I was further divided by symptoms: claudication in 10 extremities, rest pain in 17 extremities, and gangrene in 7 extremities. Group II was composed of 11 patients with abdominal aortic aneurysm in which resection was technically impossible, and 11 patients who developed sepsis of a previously inserted aortic prosthesis. All patients had received antistaphylococcal antibiotics preoperatively.

There were 17 males and 8 females in Group I. Females were operated on at a statistically significant earlier age than males, 57.5 years vs. 68 years ($p < 0.01$). There were 19 males and 3 females in Group II, both with a mean age of 65 years.

Ischemic heart disease and chronic obstructive pulmonary disease were present in 80% of the total

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

0003-4932-78-0600-0647-0075 © J. B. Lippincott Company

TABLE 1. *Early Results of Elective Extra-anatomic Bypass of Abdominal Aorta*

Operative Indication	No. of Extremities	Patent
Claudication	10	10 (100%)
Rest pain	17	15 (88%)
Gangrene	7	5 (71%)

population. Hypertension was significantly more prevalent in the female population ($p < 0.01$).

Results

The grafts remained patent for the first 30 postoperative days in 88% of the extremities of Group I patients. All ten extremities operated on for claudication improved as did 20 of 24 extremities (83%) operated upon for limb salvage (Table 1). The in-hospital postoperative mortality rate was 4%. One patient developed acute tubular necrosis and gram negative sepsis and died of a myocardial infarction. One patient survived a postoperative myocardial infarction. Three patients required four major amputations. There were two graft infections (6%) both in the groin, one *S. aureus* involving the anastomosis, the other a superficial *E. coli* infection. The patient with the *S. aureus* infection died of sepsis (Case 2) whereas the patient with *E. coli* infection recovered with local antibiotic therapy and died 37 days later of an unrelated myocardial infarction (Case 1).

The in-hospital mortality rate for Group II patients was 41% and was due to the high incidence of multisystem failure manifested by acute tubular necrosis, pneumonia, and gram negative sepsis. Eight patients developed ATN, one survived; seven patients developed sepsis, one survived; and, six patients developed pneumonia and two survived. There were four graft infections (10.8%) in patients without antecedent sepsis, necessitating graft removal. The first patient, (Case 3) developed a *S. aureus* infection of the midportion of his right axillobifemoral graft, 30 days following operation for a ruptured abdominal aortic aneurysm. This portion was excised at the time of diagnosis and a contralateral axillobifemoral graft was inserted. This patient died two years later of a myocardial infarction with a patent graft and two viable extremities. The second patient, (Case 4), developed a *S. aureus* infection at the left groin anastomosis eight days following bilateral axillofemoral grafts for a ruptured abdominal aortic aneurysm with a congenital left sided inferior vena cava. The left axillofemoral graft was removed 28 days after diagnosis of the infection and the patient died 12 days later with a viable left lower extremity of ATN and pneumonia. The third patient, (Case 5), developed a mixed *S. aureus*, *E. coli* infection at the right groin anastomosis 11 days following bilateral axillofemoral grafts for a ruptured abdominal aortic aneurysm. The graft was removed three days following diagnosis of infection, the right lower extremity was amputated above the knee one day following graft removal, and the patient died of gram negative sepsis 13 days after amputation. The fourth patient, (Case 6), developed a *P. aeruginosa* infection at the right groin anastomosis seven months following bilateral axillofemoral graft for an aortoduodenal fistula. An infected false aneurysm at the right groin anastomosis was resected and a new graft segment was inserted distally to the superficial femoral artery. The patient is alive with a patent graft five years following initial operation. For all graft infections five of six grafts were removed (83%), one of six limbs were lost, three of five limbs required another extra-anatomic bypass to a clean arterial segment, and three of six patients died (Table 2).

The immediate operative failure rates were similar for both groups. In Group I five of 33 grafts (15%) thrombosed within the first three postoperative days, and in Group II five of 37 grafts (13.5%) thrombosed in the same time period. Of those grafts that remained patent longer than three days, the one year patency rate determined by the life table analysis of Cox and Kaplan and Meier was significantly greater in Group I patients, 83.5% than in Group II, 47%.[2,9] ($p < 0.01$) At two years the graft patency rate in Group I patients determined by this life table analysis was 60% (Fig. 1).[2,6,9] Therefore, the rate of graft thrombosis as determined by life table analysis in the electively treated patients was 16.5% for the first year and 23.5% for the second year.

Postoperative graft thrombosis occurred in 18 grafts (26%); six in the immediate postoperative period, five in the first three months, three in the first year, and four in the second year. Thrombectomy under local anesthesia was attempted in 11 occluded grafts (Table 3). Patency was re-established in three of five prostheses

TABLE 2. *Results of Treatment for Postoperative Graft Infection*

Patient	Graft	Limb	Life
1	Saved	Survived	Survived
2	Lost	Saved*	Dead
3	Lost	Saved*	Survived
4	Lost	Survived	Dead
5	Lost	Lost	Dead
6	Lost	Saved*	Survived
Total:	5 of 6 removed (83%)	1 of 6 lost*	3 of 6 dead (50%)

* Three of 5 surviving limbs required another bypass to a clean segment.

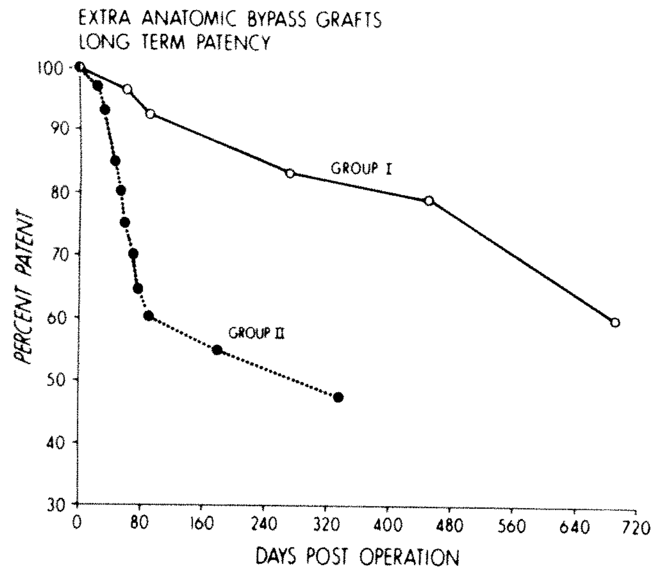


FIG. 1. Long-term patency of Group I and Group II bypass grafts by Life Table analysis.

that occluded in the immediate postoperative period. The failures required amputation. The three successfully thrombectomized grafts remained patent for 17.2 months, ten days, and ten days. The latter two grafts were in a patient who died ten days after operation of a myocardial infarction. Thrombectomy was attempted on two grafts that occluded at 9.5 months and 20.5 months and although initially successful for one and two months, thrombosis recurred requiring amputation in one patient and revascularization via a contralateral axillofemoral bypass graft in the other. Three other patients with late graft occlusion at three, three, and 11 months have undergone two to five successful thrombectomies with cumulative patencies of 5.5, 18.5, and 44.5 months.

Thrombectomy was not attempted in seven occluded grafts (Table 4). Three of these occurred in the early postoperative period and two required major amputation. The other four grafts occluded at four, 14, 15, and 23 months and required contralateral axillofemoral bypass grafts for limb preservation. All were successful (Table 4).

Discussion

The cumulative experience with extra-anatomic bypass grafts of the abdominal aorta since their initial description in 1962–1963 by Blaisdell and Louw confirms their usefulness in providing adequate blood flow to ischemic lower extremities.[1,11] Used electively in poor risk patients with aorto-iliac occlusive disease, we obtained an initial success rate of 83% when operation was for limb salvage and 100% when operation was for claudication. This compares favorably with the results of Mannick and Moore who reported success rates of 87 and 94%.[12,15] Moore also reports a success rate of 80% in patients with claudication.[15] Despite the high incidence of serious associated disease, our elective operative mortality rate was 4%. Others have reported a postoperative mortality rate of 2.7, 4.7 and 5%[10,13,15] indicating the relative safety of this operation in the poor risk patient. In good risk patients the postoperative mortality of aorto-femoral bypass is reported as 8.6% and that for endarterectomy as 3%.[3,14] When intra-abdominal aortic reconstruction is technically impossible, as in our Group II patients, the extra-anatomic bypass graft is the only operative alternative. The postoperative mortality rate of 41% in our series and 25–100% in other series indicate the critical nature of the underlying disease process in these patients who die of multisystem failure manifested by shock, gram negative sepsis, and acute tubular necrosis.[10,12,13,15]

Our incidence of graft infection was 6% in the elective group and 10.8% in the emergent group. This is higher than the rate of 3% reported by Szilagyi for aorto-femoral and femorofemoral bypass (51 of 1354 grafts)[18] and 3.2% reported by Jamieson, et al., for prosthetic grafts with a groin incision (ten of 315 grafts). Treatment of graft infection required removal

TABLE 3. *Thrombosed Grafts Treated by Thrombectomy*

Patient	Indication	Day of Thrombosis	Treatment	Result	Remarks
1	Ruptured AAA	11 mo, 13 mo, 13.5 mo, 7 mo	Thrombectomy X5	Patent 44.5 mo	Alive, patent grafts
2	Graft sepsis	3 mo, 2 mo, 0.5 mo	Thrombectomy X3	Patent 5.5 mo	Dead, patent at death
3	Ruptured AAA	1 day	Thrombectomy	Patent 10 days	Dead, patent at death
4	Ruptured AAA	1 day	Thrombectomy	Patent 10 days	Dead, patent at death
5	Claudication	20.5 mo	Thrombectomy	Patent 2 mo	Alive, additional graft patent
6	Rest pain	1 day	Thrombectomy	Thrombosed	Amputation
7	Rest pain	1 day	Thrombectomy	Patent 17.2 mo	Thrombosed, amputation
8	Rest pain	2 mo	Thrombectomy	Patent 11 mo	Alive, patent graft
9	Gangrene	1 day	Thrombectomy	Thrombosed	Amputation
10	Gangrene	3 mo, 2 mo	Thrombectomy X2	Patent 18.5 mo	Dead, patent at death
11	Gangrene	9.5 mo	Thrombectomy	Thrombosed	Amputation

TABLE 4. *Thrombosed Grafts Without Thrombectomy*

Patient	Indication	Day of Thrombosis	Treatment	Result	Remarks
1	Rest pain	4 mo	Cont. axillo femoral	Patent 9 mo	Alive, patent graft
2	Rest pain	15 mo	Ipsl. axillo femoral	Patent 1.5 mo	Sepsis 2° to infection
3	Rest pain	1 mo	Bil. aorto femoral	Patent 1 mo	Dead, patent at death
4	Rest pain	2 mo	No treatment	Thrombosed	Alive, additional graft thrombosed
5	Rest pain	23 mo	Cont. axillo femoral	Patent 14 mo	Alive, patent graft
6	Gangrene	1 day	No treatment	Thrombosed	Amputation
7	Claudication	14 mo	Cont. axillo femoral	Patent 39 mo	Dead, patent at death

of five of six grafts and revascularization into a clean arterial segment in three of five extremities. This resulted in limb salvage in five of six cases, and there was a mortality rate of 50%. Our high incidence of groin wound infection occurred despite the prophylactic use of antibiotics.[7]

Although early satisfactory results are obtained in the poor risk patient with aorto-iliac occlusive disease by extra-anatomic graft, long-term patency does not compare favorably with that of intra-abdominal bypass.[4,14,17] Aorto-femoral bypass with dacron has been shown to give a 97% six year patency rate.[14] Of 102 patients undergoing aorto-iliac thromboendarterectomy, a 100% patency rate was noted in 38 patients followed five years.[3] A 98% patency rate was also noted in 97 patients followed four to 36 months in the same series.[3] Extra-anatomic bypass grafts have shown considerably lower patency rates. In Moore's series 60% were patent at 12 months and 50% at 18 months.[15] LoGerfo, et al., determined 74% of the axillobifemoral and 37% of axillounifemoral grafts were patent at five years.[10] Unfortunately, the latter study is one where cumulative patency is measured. That is, graft thrombosis treated by successful thrombectomy is not considered a graft failure. Thus a graft is considered patent over a long period even though multiple thrombectomies have been performed. Our data has been analyzed by the life table method such that patency is described as a finite time period from operation to graft occlusion. Thrombectomy and the resulting patency period is considered a separate event. In elective cases our one year patency rate is 83.5% and our two year rate is 60%. These results are similar to other reports and likewise do not approach the patency rates described for aorto-femoral grafts or aorto-iliac thromboendarterectomy.

Group II patency rates are significantly lower than either Group I rates or those reported for aorto-femoral bypass or endarterectomy. High postoperative mortality in this group does not explain the lower patency rate of 47%. It may be related to a number of factors. These patients are admitted in shock and complete evaluation of peripheral pulses is often inadequate due to low peripheral perfusion and the necessity for rapid resuscitation and early operation. Preoperative angiography is not routine. Initial operative efforts are directed at intra-abdominal aortic repair that often results in aortic ligation. This is followed by rapid axillofemoral bypass grafting in the setting of a critically ill, deteriorating patient. Thus technique and prolonged low peripheral perfusion may combine to significantly lower patency rates in those patients who do survive.

As noted above, one study calculates cumulative long-term patency in which thrombectomy provides prolongation of graft life.[10] Postoperative thrombosis has been reported in 12, 20, and 28% of cases.[10,12,13] A 26% thrombosis rate is reported in this series. Most graft thromboses occur in the early postoperative months. An explanation of early graft thrombosis has been suggested by Mannick.[13] The neointima forms during this period as does the surrounding fibrous capsule. Both provide a greater capacity to eventually withstand temporary periods of reduced flow. Thrombectomy is the treatment of choice in the event of graft thrombosis. It may be done under local anesthesia and should be followed by infraoperative angiography to define distal runoff. It may be necessary to improve runoff with additional distal grafts.[10] Revascularization via contralateral axillofemoral graft or femoro-femoral graft should also be considered. In four instances flow through patent hypogastric arteries to the affected limb has resulted in limb salvage. Failure to perform a thrombectomy or additional bypass grafts resulted in amputation in five of 18 cases.

References

1. Blaisdell, F. W. and Hall, A. D.: Axillary-Femoral Artery Bypass for Lower Extremity Ischemia. Surgery, 54:563, 1963.
2. Cox, D. R.: Regression Models and Life Tables (with discussion). J. R. Statist. Soc., 34:187, 1972.
3. Darling, R. C. and Linton, R. R.: Aortoiliofemoral Endarterectomy for Atherosclerotic Occlusive Disease. Surgery, 55: 184, 1964.
4. DeBakey, M. E., Crawford, E. S., Cooley, D. A. and Morris, G. C., Jr.: Surgical Considerations of Occlusive Disease of the Abdominal Aorta and Iliac and Femoral Arteries: Analysis of 803 Cases. Ann. Surg., 148:306, 1958.

5. DeWeese, J. A. (discussion) Plecha, F. R. and Pories, W. J.: Extra-anatomic Bypasses for Aortoiliac Disease in High-Risk Patients. Surgery, 80:486, 1976.
6. Gehan, E. A.: A Generalized Wilcoxon Test for Comparing Arbitrarily Single Censored Samples. Biometrika, 52:203, 1965.
7. Hunt, T. K., Alexander, J. W., Burke, J. F. and MacLean, L. D.: Antibiotics in Surgery. Arch. Surg., 110:148, 1975.
8. Jamieson, G. G., DeWeese, J. A. and Rob, C. G.: Infected Arterial Grafts. Ann. Surg., 181:850, 1975.
9. Kaplan, E. L. and Meier, P.: Non Parametric Estimation from Incomplete Observations. J. Am. Statist. Assoc. 53: 457, 1958.
10. LoGerfo, F. W., Johnson, W. C., Corson, J. D., et al.: A Comparison of the Late Patency Rates of Axillobilateral Femoral and Axillounilateral Femoral Grafts. Surgery, 81, 33, 1977.
11. Louw, J. H.: Splenic-to-Femoral and Axillary-to-Femoral Bypass Grafts in Diffuse Atherosclerotic Occlusive Disease. Lancet, 1401, June 29, 1963.
12. Mannick, J. A. and Nabseth, D. C.: Axillofemoral Bypass Graft. A Safe Alternative to Aortoiliac Reconstruction. N. Engl. J. Med., 278:461, 1968.
13. Mannick, J. A., Williams, L. E. and Nabseth, D. C.: The Late Results of Axillofemoral Grafts. Surgery, 68:1038, 1970.
14. Moore, W. S., Cafferata, H. T., Hall, A. D. and Blaisdell, F. W.: In Defense of Grafts Across the Inguinal Ligament: An Evaluation of Early and Late Results of Aorto-Femoral Bypass Grafts. Ann. Surg., 168:207, 1968.
15. Moore, W. S., Hall, A. D. and Blaisdell, F. W.: Late Results of Axillary-Femoral Bypass Grafting. Am. J. Surg., 122: 148, 1971.
16. Plecha, F. R. and Pories, W. J.: Extra-Anatomic Bypasses for Aortoiliac Disease in High-Risk Patients. Surgery, 80:480, 1976.
17. Szilagyi, D. E., Smith, R. F., Elmquist, J. G., et al.: Angioplasty in the Treatment of Peripheral Occlusive Arteriopathy. Arch. Surg., 90:617, 1965.
18. Szilagyi, D. E., Smith, R. F., Elliott, J. P. and Vrandecic, M. P.: Infection in Arterial Reconstruction with Synthetic Grafts. Ann. Surg., 176: 321, 1972.
19. Szilagyi, D. E., Elliott, J. P., Smith, R. F., et al.: Secondary Arterial Repair: The Management of Late Failures in Reconstructive Arterial Surgery. Arch. Surg., 110:485, 1975.
20. Vetto, R. M.: The Femorofemoral Shunt: An Appraisal. Am. J. Surg., 112:162, 1966.

DISCUSSION

DR. WILLIAM H. EDWARDS (Nashville, Tennessee): (Slide) At the vascular meetings this past summer, we presented a series of 1700 vascular procedures of which 67 were extra-anatomic bypass; these were both femoro-femoral as well as axillo-femoral bypass grafts. Seven of these patients had to be returned to the operating room within 72 hours following the original surgery. Five of these seven were for thrombosis; two were for hemorrhage.

Of the patients returned to the operating room for thrombosis, the graft was opened in only two: one requiring thrombectomy and one a profundoplasty.

(Slide) In the total group of 1700 patients, there were 58 that were returned to the operating room for thrombosis with a much higher salvage rate of return of flow. The patients with aortic bypass had a higher patency rate than those with extra-anatomic bypasses or embolectomies.

We agree that the patient in whom some time and effort has been invested for restoration of flow to the lower extremities should have a second effort if the patient's general condition allows this. We prefer technically to approach both suture lines at the second operation feeling that there is probably some problem at a suture line or at the anastomosis which has caused the thrombosis. Fortunately, we have not had a high incidence of sepsis and consequently have not had to perform extra-anatomic bypasses for that reason.

DR. GEORGE JOHNSON, JR. (Chapel Hill, North Carolina): The extra-anatomic bypass graft has certainly contributed to our management of arterial occlusion. They are not only useful in the axillo-femoral and the femoro-femoral position, but also between the two axillary arteries and the carotid and subclavian arteries.

We are able to take blood from one vascular system to give to another, because the flow through the arteries depends more on the peripheral resistance of the vascular bed than it does on the size of the artery. Thus each system has considerable reserve. The "rob Peter to pay Paul" principle works very well, as long as Peter, the artery that's being robbed, has no proximal obstruction.

It is, however, possible to cause distal ischemia in the system from which you take the blood, if proximal arterial occlusion is present. We have seen this in two cases; thus we have made the good leg bad.

In his manuscript, Dr. DeWeese quite properly emphasizes dangers of infection in the subcutaneously planted graft. This is a distressing event, especially when you have done the operation on a poor-risk patient, or a patient with an infected graft from another location, and are looking for a simple procedure.

The main point of the paper is that, although there is a high incidence of thrombosis, Dr. DeWeese has demonstrated that if a thrombectomy, or further attempts at revascularization are performed, a successful outcome frequently results. With this I agree.

In North Carolina Memorial Hospital in Chapel Hill we performed 42 axillofemoral bypass grafts, with similar results to those just reported.

Two technical points: first, the 8 mm graft works better in our hands, since the velocity of flow is greater, and, we think, has less tendency to clot. Second, the axillary to both femorals has better results than to one femoral—also, we suspect, because of the increased velocity in the long limb of the graft.

One question: Does your method of analysis do your results justice? You may increase the number of grafts exposed to the risk of clotting, but in doing this you double expose the grafts that do not function, or in which you have had to do another revascularization procedure. This would not give us a true incidence of primary graft failure, which should be better than the results that you report.

I think we need to emphasize that these are not the procedures of choice for aortic or iliac occlusive disease. Replacement of bypass of an aorticoiliac segment with a prosthetic graft gives excellent early and late results, and can be performed with a low mortality in a majority of these patients. Extra-anatomic bypass grafts, as just described, are for patients with infected grafts, or who are very poor risk.

DR. W. STERLING EDWARDS (Albuquerque, New Mexico): We have used these techniques infrequently, for two reasons. First, we have been very fortunate in not having many infected grafts. Secondly, we've been rather reluctant to use axillo-femoral grafts on elective patients, since the reported long-term patencies have been rather poor. Therefore, I have more questions than comments.

My first question is: Was there any difference in patency rate, depending on whether a woven or knitted graft was used? It is stated in the manuscript that both types were used with equal frequency.

Secondly, at the time of thrombectomy, to reopen occluded grafts, was an intraoperative arteriogram performed, to see if there was any correctable defect at either anastomosis?

Thirdly, I'm not quite sure what is meant by an "inoperable abdominal aneurysm." Aneurysms can be replaced with the usual technique of grafting in almost all cases.

Fourthly, one surprise to me is that Group II, the emergency procedures, apparently—those patients with aneurysms—had poorer long-term patency of the grafts than did Group I, the patients with occlusive disease. This is a little bit of a surprise. I would expect the patients with aneurysms, with, presumably, patent distal arteries, to have a long-term better patency rate. Is there an explanation for this?

Dr. Robert W. Oblath (Closing discussion): The infection rate for the cumulative study of the 71 grafts was approximately 8½%. The Group I rate was 6%, and the Group II rate was 10.8%. All patients were started on antistaphylococcal antibiotics preoperatively. The rates are higher than either Szilyagi reports, at 3%, or DeWeese reports, at 3.2%, with grafts with a groin incision. We have no adequate explanation for that infection rate.

In answer to the question about graft size, we use 10 mm grafts. We find that they remain patent, and we do not have experience with 8 mm grafts at our institution.

We currently are using, or going to use, axillobifemoral grafts, because they have demonstrated consistently higher flows from the axillary anastomosis, and we believe that their patency rates will probably be better than the axillounifemoral grafts.

Further, we believe that the incidence of cardiac disease, compounded by diabetes mellitus, limits patient survival, and, therefore, the grafts are usually patent at the time of death.

As far as the thrombosis rate is concerned, there were 47 woven grafts and 24 knitted grafts. The rate of thrombosis was in the same statistical proportion between knitted and woven. Therefore, there can be no statistically obvious difference between the grafts and their thrombosis rate.

By "complicated abdominal aneurysm"—we have had a number of problems with the proximal anastomosis, and what we refer to as a complicated abdominal aortic aneurysm precluding resection is an aneurysm which has been resected, and then either a posterior tear through or between the renal arteries or dissolution of the anastomosis occurs, with a massive hemorrhage requiring ligation of the aorta.

In addition, we have had two cases of left-sided inferior vena cavas crossing anterior to the aneurysm, which precluded resection of the abdominal aortic aneurysm. Thus, grafts were placed extra-anatomically.

All thrombectomized grafts have been associated, or been followed by, angiography at the time of surgery. The long-term patency of Group II is considerably lower than that in Group I. We don't believe that Group I should be compared to Group II for long-term patency, because we believe that technical problems in a severely ill, debilitated, deteriorating patient at the time of operation limit the patency of the graft in Group II.

T.E.D.®

Full Leg Anti-Embolism Stockings

- **Side panel and waist belt assure reliable continuous non-slip protection**
- **Graduated compression from ankle to upper thigh – insures optimum blood flow**
- **Seamless construction to eliminate harsh ridges**
- **Pressure break protects critical popliteal area and insures free movement**
- **Contoured instep provides flexibility for patient exercise**
- **Inspection toe opening provides easy access for medical examination**

KENDALL
INNOVATORS IN PATIENT CARE

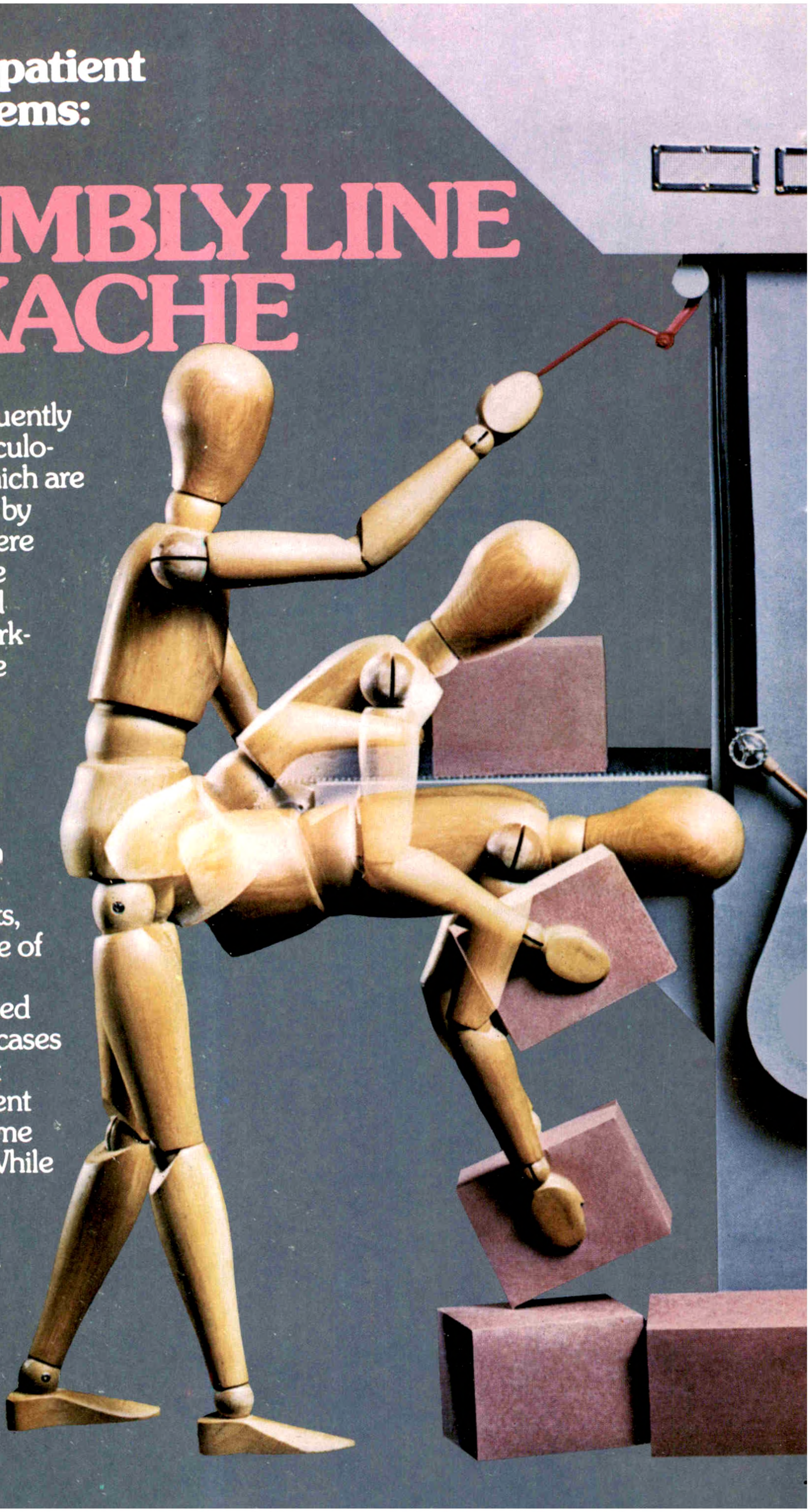
Contraindications: Stockings may not be recommended for patients with the following: **1.** Any local leg condition in which stockings would interfere, such as: **a.** dermatitis, **b.** vein ligation (immediate post-operative), **c.** gangrene, **d.** recent skin graft. **2.** Severe arteriosclerosis or other ischemic vascular disease. **3.** Massive edema of legs or pulmonary edema from congestive heart failure. **4.** Extreme deformity of leg. **5.** For thigh length, patients with a circumference greater than 25 in. (63.5cm) at the gluteal furrow. For full-leg (X-S,S,M,L), patients with a circumference of 25 in. (63.5cm) or greater at the gluteal furrow. For full-leg (X-L), patients with a circumference greater than 32 inches (81.3cm) at the gluteal furrow.
Precautions: 1. Proper sizing and application must be assured. **2.** For full-leg style T.E.D. Stockings avoid interference of side panels or waistband with incisions, drainage tubes, catheters or other exterior devices.
Warnings: Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

© 1978, The Kendall Company ■ Hospital Products ■ One Federal Street ■ Boston, MA 02101

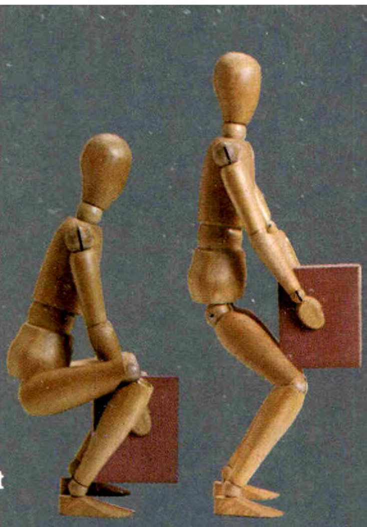
the low-back patient and his problems:

ASSEMBLY LINE BACKACHE

Chances are you frequently see patients with musculoskeletal conditions which are caused or aggravated by assembly line jobs where they must perform the same activity over and over again. Those workers whose jobs require repetitive lifting or bending are most likely to complain of low-back discomfort. Unnatural motions repeated for hours on end can place undue strain on the ligaments, muscles and vertebrae of the lower back, even though the objects lifted are not heavy. These cases are especially difficult to manage if the patient must return to the same job after treatment. While he can't avoid lifting altogether, he can benefit from practical instructions on the correct way to lift and suggestions on how to break up his routine.



Lift with the legs, never the back
This rule applies, even when picking up a scrap of paper. The patient should never bend forward or sideways from the waist, or lift from a bending-forward position. He will better understand why it is important to let the legs do the lifting if you explain that those strong bones and powerful muscles can withstand the strain far better than 24 movable vertebrae in a curved line. You may find it helpful to demonstrate the correct way to lift. Squat in front of the object keeping it close to the body. Then slowly rise to a standing position. The patient should never lift with his legs straight.



Advice to all low-back patients
Avoid lifting objects from car trunks, reaching over furniture to open windows, etc. Don't make beds or run the vacuum cleaner when the back is "acting up." If the patient's job requires repetitive lifting or bending, he should follow correct procedures and periodically take a rest to break up his routine. He may be able to perform the work seated or standing with one foot resting on a small stool. Perhaps his employer can find something different for him to do occasionally. If his back continues to bother him, he will probably have to consider getting a different kind of job.

as an adjunct in the relief of discomforts associated with acute, painful musculoskeletal conditions

ROBAXIN®-750
(Methocarbamol, NF)

750 mg capsule-shaped tablets

the Robaxin regimen:

Bed
Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort.

Board
Have patient insert section of ½" or ¾" plywood between mattress and box springs.

Heat
The judicious use of moist heat is often very beneficial.

Robaxin-750 can relieve the discomforts associated with acute musculoskeletal conditions. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.
It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk. Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.
Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

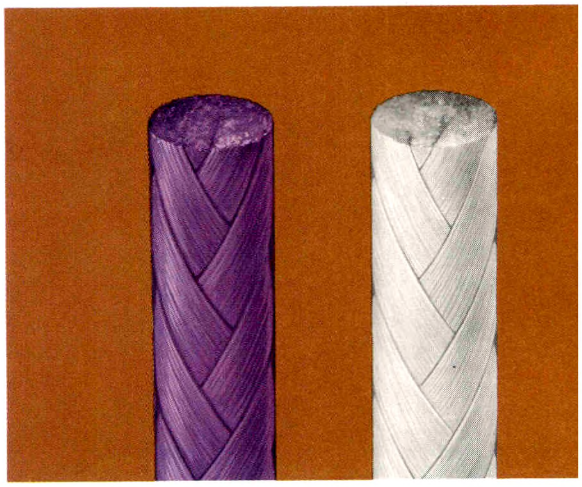
A. H. Robins Company, Richmond, Va. 23220
A·H·ROBINS

ETHICON DOES IT AGAIN

VICRYL* (Polyglactin 910) suture

Improved braided construction results in:

Superior smoothness
Better knot security
Improved handling characteristics
—In addition to the other benefits VICRYL suture is known for. Available dyed and undyed on a wide variety of needles.



Available braided, dyed and undyed.

ETHICON
the closing word

*Trademark

(See next page for complete product information.)

© ETHICON, INC. 1978

Revised 6/77

VICRYL* (Polyglactin 910) suture

COMPLETE PRODUCT INFORMATION

VICRYL* (Polyglactin 910) Synthetic Absorbable Suture

DESCRIPTION VICRYL (polyglactin 910) synthetic absorbable suture is prepared from a copolymer of glycolide and lactide. These substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

VICRYL sutures are sterile, inert, nonantigenic, nonpyrogenic, and elicit only a mild tissue reaction during absorption. The braided and monofilament sutures are colored violet to enhance visibility in tissue. The braided suture is also available undyed (natural).

ACTIONS Two important characteristics describe the *in vivo* behavior of absorbable sutures: first, tensile strength retention, and second, the absorption rate (loss of mass).

Subcutaneous tissue implantation studies of VICRYL suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of VICRYL suture is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

INDICATIONS VICRYL synthetic absorbable suture is intended for use as an absorbable suture or ligature.

CONTRAINDICATIONS This suture, being absorbable, should not be used where extended approximation of tissues under stress is required.

WARNINGS The safety and effectiveness of VICRYL (polyglactin 910) suture in neural tissue, and in cardiovascular surgery have not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize.

PRECAUTIONS VICRYL suture knots must be properly placed to be secure. Place the first throw in precise position for the final knot, using a double loop; tie the second throw square, using horizontal tension; additional throws are advisable.

Skin and conjunctival sutures remaining in place longer than 7 days may cause localized irritation and should be removed as indicated.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

ADVERSE REACTIONS Reactions reported in clinical trials which may have been suture related have been minimal. These include skin redness and induration, rare instances of hemorrhage, anastomotic leakage, wound separation in the eye, and abscesses.

DOSAGE AND ADMINISTRATION Use as required per operation.

HOW SUPPLIED VICRYL sutures are available sterile, as braided dyed (violet) and undyed (natural) strands in sizes 3 to 8-0, in a variety of lengths, with and without needles, and on LIGAPAK® ligating reels. VICRYL sutures, monofilament, dyed (violet) are available in sizes 9-0 and 10-0, in a variety of lengths with needles.

Also available in sizes 1 to 4-0 attached to CONTROL RELEASE® needles.

Trademark

ETHICON

FACULTY POSITIONS

College of Medicine, King Faisal University
Dammam, Saudi Arabia

Applications invited from qualified men and women in General Surgery. American Board certification in surgery (or equivalent in Canada or Great Britain) plus teaching experience required. Language of instruction is English. Positions available in September 1978; interviews scheduled with the Dean in the United States early in 1978.

Salary ranges: (Given monthly in Saudi Riyals followed by approximate annual equivalent in U.S. dollars)

	Academic Salary	+	*Clinical Bonus* of 50%	=	*Total Approximate yearly dollars*
Professor:	SR 6,000-6,600		SR 3,000-3,300		($30,500-33,500)
Assoc. Prof.:	SR 4,800-5,800		SR 2,400-2,900		($24,400-29,400)
Assist. Prof.:	SR 3,600-4,600		SR 1,800-2,300		($18,300-23,400)

Benefits include free furnished accommodations and annual leave with travel allowance to country of origin.

No Saudi income tax is imposed.

Send curriculum vitae and references with addresses and telephone numbers to:

Mohammed T. Altorki, M.D., MRCP
Dean of the Medical Faculty
King Faisal University
c/o Saudi Arabian Educational Mission
2223 West Loop South, Suite 400
Houston, Texas 77027

Specify dates of teaching appointments and availability.

EMERGENCY ROOM PHYSICIAN

A private, non-profit community hospital situated north of Boston is in need of a physician to assist them in leading and establishing a group to cover emergency medical services in a modern setting. Arrangements are open.

Please forward curriculum vitae, in confidence, to:

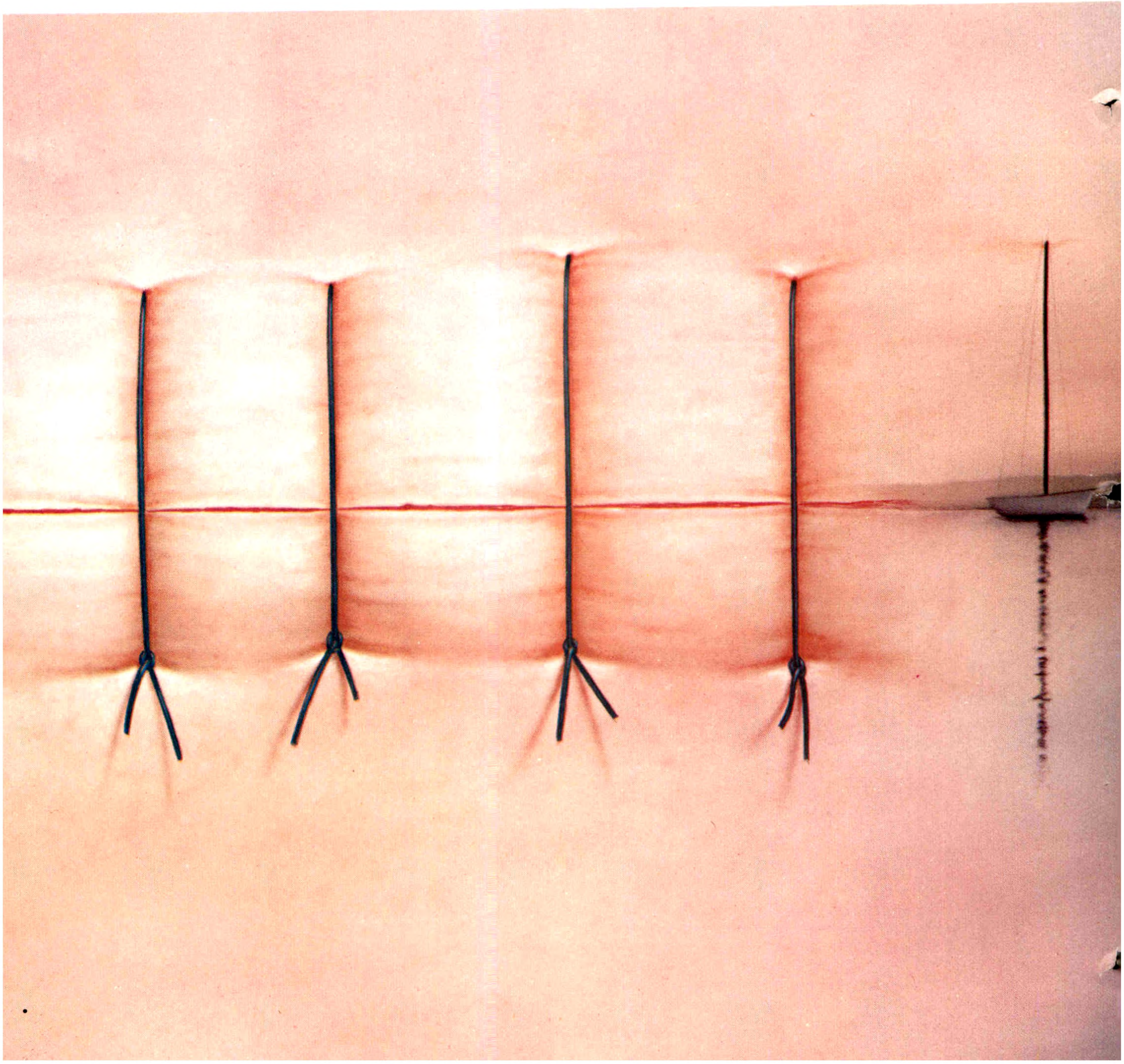
Search Committee
BOX ANN6A
J. B. Lippincott Company
East Washington Square
Philadelphia, PA 19105

An Equal Opportunity Employer

"...it has long been recognized that anxiety, tension, agitation, and apprehension are all capable of increasing pain perception..."

Halpern, L. M.: Anxiety and pain in postoperative patients. Hospital Practice (special report) January 1977, pp 31-33.

Following surgery... the perception of pain diminished

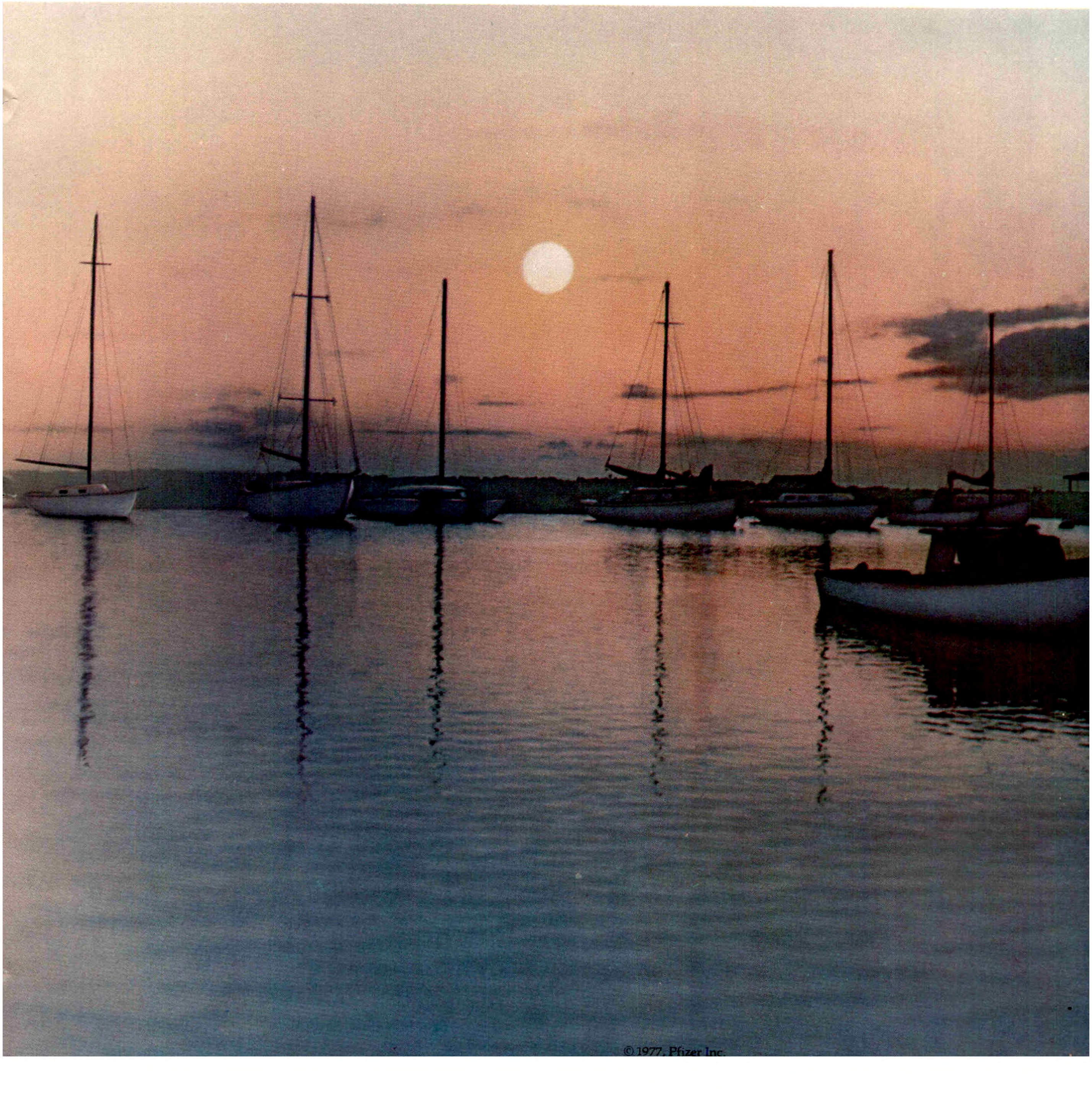


Vistaril® I.M.
(hydroxyzine HCl)

by Calm

- reduces the anxiety component of pain
- permits reduction in narcotic dosage
- controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



© 1977, Pfizer Inc.

Vistaril® I.M.
(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

preoperatively and postoperatively

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml—10 ml vials; 50 mg/ml—2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml—1 ml fill; 100 mg/2 ml—2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

Pfizer
LABORATORIES DIVISION
PFIZER INC

Tablets
Percodan® CII

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

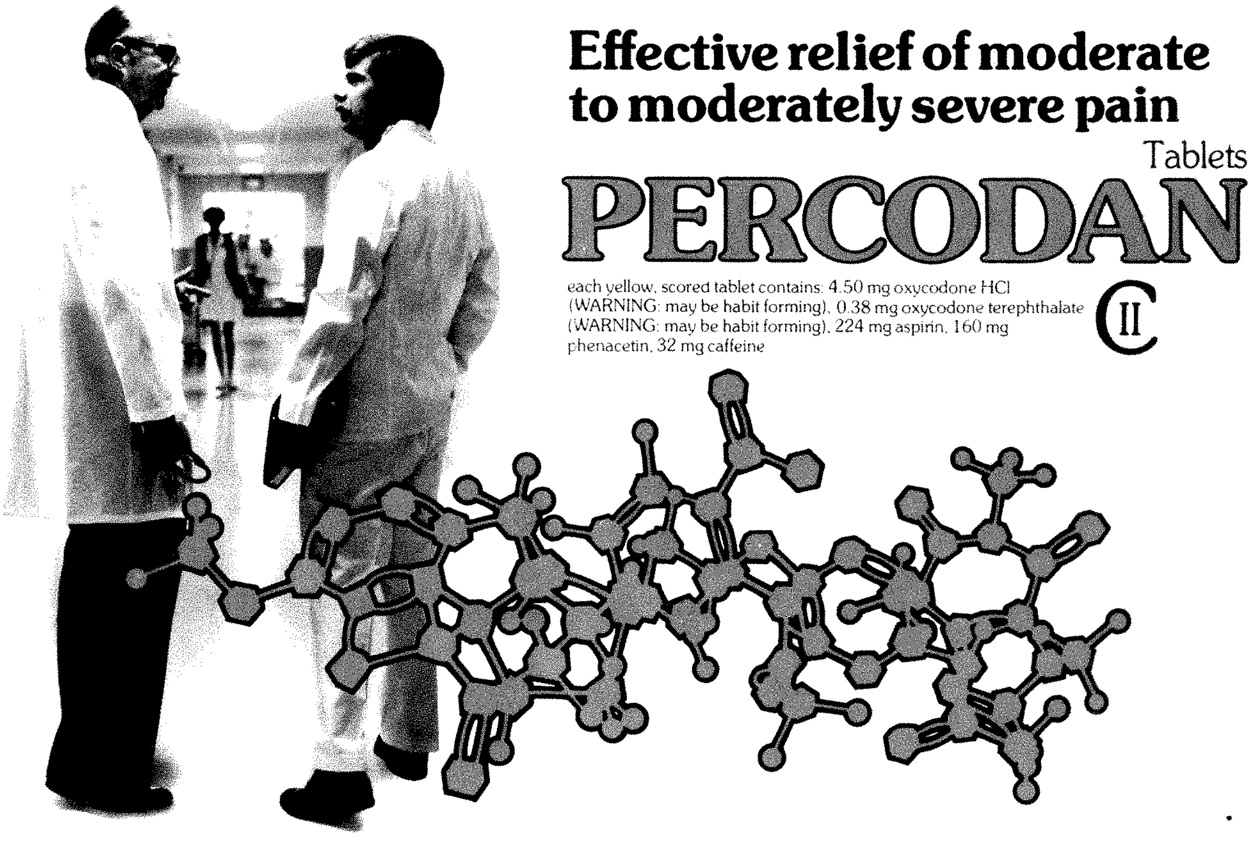
Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories, Inc.
Subsidiary of the DuPont Company

DUPONT

CONSIDERATIONS FOR ORAL NARCOTIC ANALGESIC USE:

1. **Determine need** — What is causing pain? How is it perceived by you and your patient?
2. **Prescribe a rapid-acting agent** — Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.
3. **Minimize potential risk** — Prescribe in limited quantities for selected patients.

   Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.
4. **Provide adequate analgesia with minimum doses** — Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



Effective relief of moderate to moderately severe pain

Tablets

PERCODAN

each yellow, scored tablet contains: 4.50 mg oxycodone HCl (WARNING: may be habit forming), 0.38 mg oxycodone terephthalate (WARNING: may be habit forming), 224 mg aspirin, 160 mg phenacetin, 32 mg caffeine

CII

PERCODAN® is a registered trademark of Endo Inc.

Please see facing page for Brief Summary of prescribing information.

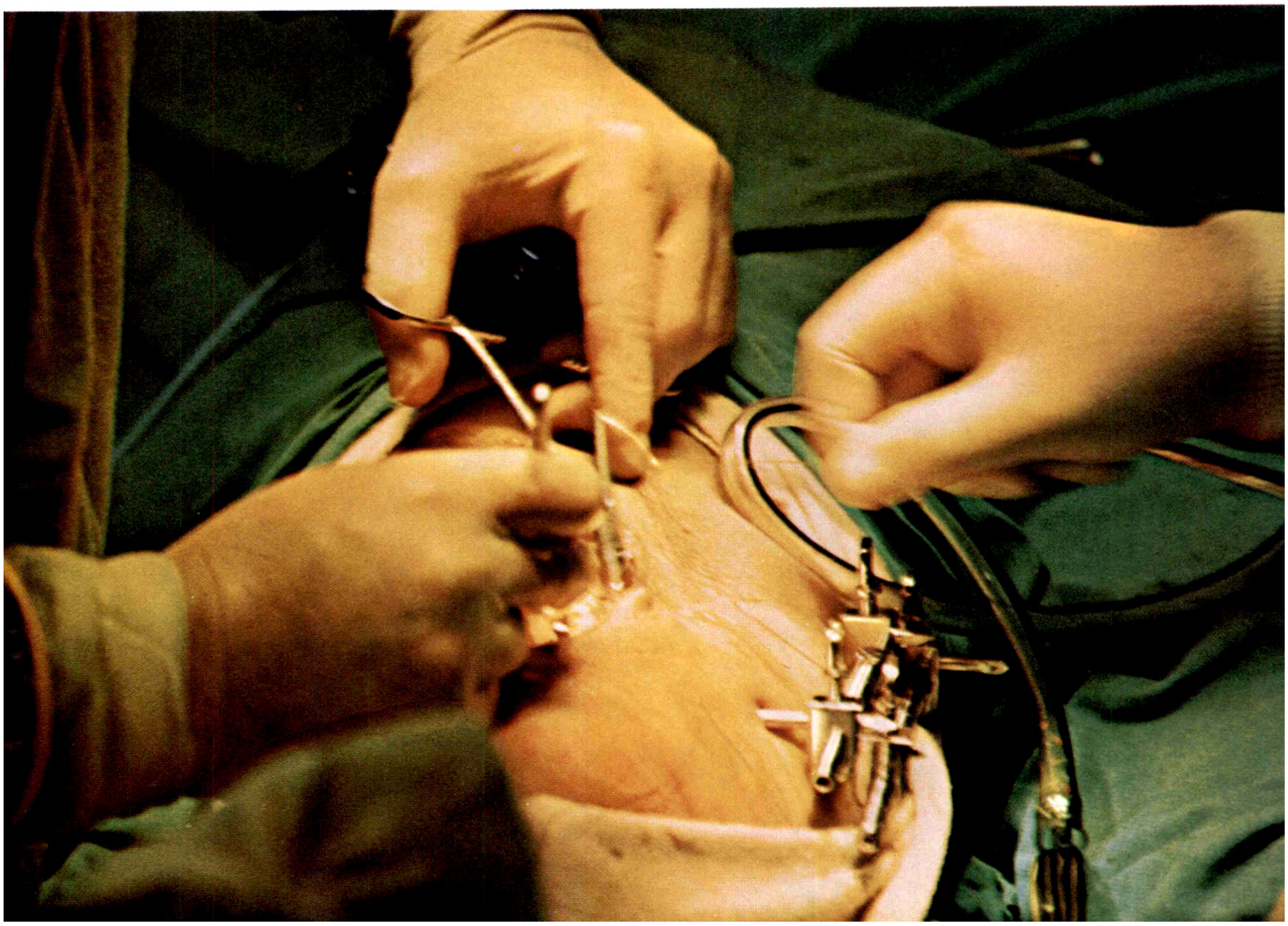
In your patients...

Experience the benefits of Nebcin® I.M./I.V.

80 mg.* in 2-ml. ampoules

*Equivalent to tobramycin.

tobramycin sulfate



in
treating
peritonitis[†]

In patients with peritonitis in whom you suspect septicemia *and the gram-negative organism isolated from blood is likely to be susceptible to tobramycin in your hospital setting*...you may start therapy with Nebcin before you receive results of susceptibility studies.[‡] In this situation, Nebcin may be a great help to you and gain valuable time for your patient.

In proper indications and recommended dosages, the general effectiveness of Nebcin is well-known. Experience its benefits in treating your patients who have peritonitis caused by susceptible strains of the indicated gram-negative organisms.

◆ I.M./I.V.
Nebcin®
tobramycin sulfate
for serious gram-negative infections in your hospital

Lilly
700152

[†] Due to indicated susceptible organisms.

[‡] The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the Warnings box on the next page.

Please see following page for summary of prescribing information.

Nebcin® ♦ I.M./I.V.
tobramycin sulfate

Summary of Prescribing Information

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: See WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg./Kg.). The possibility that prolonged or secondary apnea may occur should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

The usual duration of treatment is seven to ten days.

Usual dosage for adults, children, and older infants (normal renal function)—
3 mg./Kg./day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg./Kg./day administered in three or four equal doses. This dosage should be reduced to 3 mg./Kg./day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—
Up to 4 mg./Kg./day may be given in two equal doses every twelve hours.

Dosage guidelines for adult or pediatric patients with reduced renal function—
After a loading dose of 1 mg./Kg., subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.* To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg./Kg. q. (6 × serum creatinine) h.

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of twenty to sixty minutes.

---

*An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function
(Dosage at Eight-Hour Intervals)

For Patient Weighing		Usual Dose for Serious Infections 1 mg./Kg. q. 8 h. (Total, 3 mg./Kg./day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg./Kg. q. 8 h. (Total, 5 mg./Kg./day)	
Kg.	Lb.	**mg./dose q. 8 h.**	**ml./dose**†	**mg./dose q. 8 h.**	**ml./dose**†
120	264	120 mg.	3 ml.	200 mg.	5 ml.
115	253	115 mg.	2.9 ml.	191 mg.	4.75 ml.
110	242	110 mg.	2.75 ml.	183 mg.	4.5 ml.
105	231	105 mg.	2.6 ml.	175 mg.	4.4 ml.
100	220	100 mg.	2.5 ml.	166 mg.	4.2 ml.
95	209	95 mg.	2.4 ml.	158 mg.	4 ml.
90	198	90 mg.	2.25 ml.	150 mg.	3.75 ml.
85	187	85 mg.	2.1 ml.	141 mg.	3.5 ml.
80	176	80 mg.	2 ml.	133 mg.	3.3 ml.
75	165	75 mg.	1.9 ml.	125 mg.	3.1 ml.
70	154	70 mg.	1.75 ml.	116 mg.	2.9 ml.
65	143	65 mg.	1.6 ml.	108 mg.	2.7 ml.
60	132	60 mg.	1.5 ml.	100 mg.	2.5 ml.
55	121	55 mg.	1.4 ml.	91 mg.	2.25 ml.
50	110	50 mg.	1.25 ml.	83 mg.	2.1 ml.
45	99	45 mg.	1.1 ml.	75 mg.	1.9 ml.
40	88	40 mg.	1 ml.	66 mg.	1.6 ml.

†Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules Nebcin® (tobramycin sulfate, Lilly) Injection, 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Ampoules Nebcin, Pediatric, Injection, 20 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Hyporets® (disposable syringes, Lilly) Nebcin Injection, 60 mg. (equivalent to tobramycin) per 1.5 ml., 1.5 ml., and 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., in packages of 24.

Each ml. also contains 5 mg. phenol as a preservative, 3.2 mg. sodium bisulfite, 0.1 mg. edetate disodium, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [030476B]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

700152

Vascular Reconstructive Surgery Following Myocardial Revascularization

WILLIAM H. EDWARDS, M.D., JOSEPH L. MULHERIN, JR., M.D., WILLIAM E. WALKER, M.D., PH.D.

Survivors of successful coronary bypass have a life expectancy close to normal. Myocardial infarction has been the major cause for morbidity and mortality in patients requiring surgery. Current data suggests that patients who have undergone CAB are not only acceptable risks for subsequent surgery, but may in fact have a lesser cardiac risk than the routine patient. The selection of the proper sequential surgical procedures is critical for patient survival. We reviewed 74 major vascular reconstructive procedures in 53 patients. Twenty-nine cerebrovascular procedures, 20 femoro-popliteal bypasses, aneurysmectomy nine times, and aortic bypass in 16 patients were the procedures performed. Twenty-two abdominal operations were performed with no significant morbidity or mortality. Two patients died during the postoperative period and three have subsequently died. The 48 survivors continue to do well.

From the Surgical Service of St. Thomas Hospital and the Department of Surgery, Section of Surgical Sciences, Vanderbilt University Medical Center, Nashville, Tennessee

As THE FIRST DECADE of myocardial revascularization ends, patients with good myocardial function following coronary artery bypass (CAB) are returning with significant cerebral or peripheral vascular lesions requiring reconstructive surgery. Atherosclerosis frequently involves the arteries of several major organ systems, producing significant ischemia and symptoms in each. The coexistence of coronary artery occlusive disease and peripheral, including cerebral, arterial disease has been reported to range from 15% to 55%.[9] In many instances, relief of angina increases the importance of such symptoms as leg ischemia since the patient is now limited in his exercise tolerance by claudication instead of angina. Often, too, patients and their physicians have been content to temporize over peripheral vascular symptoms since the patient's lifestyle and life expectancy have been restricted by heart disease. There is a growing recognition, however, that survivors of successful CAB, even those with advanced coronary lesions, have a life expectancy close to normal, and therefore, it may be considered worthwhile to correct other vascular problems.

The question then arises whether peripheral vascular reconstruction has an increased risk in patients who have undergone CAB. The major source of morbidity and mortality in patients undergoing peripheral vascular reconstruction is the heart.[10] To try to answer this question, we have reviewed the results of 74 vascular procedures in 53 patients performed following CAB over the past seven years. This group of patients forms the basis of this report.

Clinical Material

Forty-five men and eight women ranged in age from 42 to 72 (Fig. 1). Five patients were under 50 years of age and five were over 70 years of age. The remaining 43 were 51–70 years (22, 51–60 years and 21, 61–70 years). The vascular reconstructive procedures were performed because of significant vascular disease affecting the carotid, aortic, renal or peripheral vascular system. Carotid endarterectomy was recommended for patients with significant stenosis in the absence of symptoms.

The 53 patients in this series all had direct myocardial revascularization while three of the patients had an additional valve replacement (Fig. 2). One patient had a single LAD bypass. Seventeen patients had two vessels bypassed, 23 had a three vessel bypass, and 12 had four or more vessels bypassed.

Four patients had carotid endarterectomy during the same hospitalization following CAB. These patients were all suffering transient ischemic attacks. An axillo-femoral-femoral bypass was performed on another patient for acute peripheral ischemia on the day following myocardial revascularization (Fig. 3).

In the 48 patients, the vascular reconstruction was carried out anywhere from six months to over four

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Reprint requests: William H. Edwards, M.D., Suite 205, 4230 Harding Road, Nashville, Tennessee 37205.

0003-4932-78-0600-0653-0075 © J. B. Lippincott Company

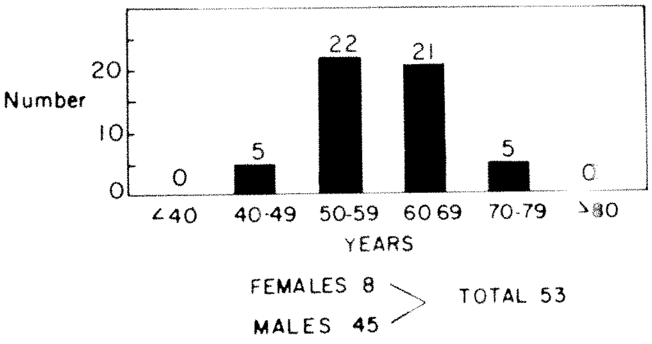


FIG. 1. Age indices.

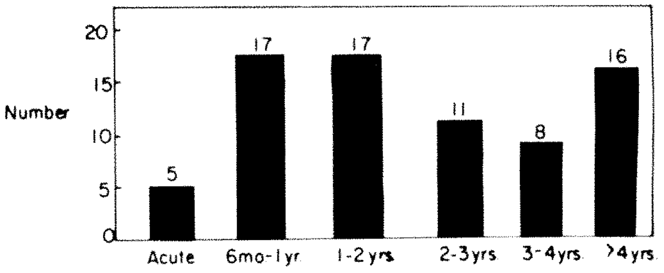


FIG. 3. Time interval.

years after CAB. In those instances in which the patient presented with initial symptoms of myocardial, as well as another major organ system involvement, the second vascular procedure was usually carried out within one year of the coronary revascularization. Twelve patients fell into this category, and 17 reconstructive procedures were performed in this group. Fifty-two operations were performed in the remaining 36 patients from one to five years after their CAB. It is this group of patients who developed significant disease of a different organ system as a result of progression of their atherosclerosis.

Carotid endarterectomy was performed 25 times for significant stenosis or symptomatic ulcerated plaques (Fig. 4). Four patients had vertebral to carotid anastomosis for vertebral stenosis. Nine patients had resection of an infrarenal abdominal aneurysm. One of these was a ruptured aneurysm.

Sixteen reconstructive procedures were undertaken for aorto-iliac and renal occlusive disease. Axillo-femoral was utilized twice and a femoro-femoral bypass on one occasion. Renal artery bypass relieved bilateral renal artery stenosis in one patient. Femoro-popliteal or femoral distal bypasses were the 20 vascular reconstructive procedures in the remaining patients.

A total of 21 patients had multiple vascular reconstructive procedures (Fig. 5). Fifteen patients had two operations, while five had three operations. One patient had an aorto-femoral bypass four years following CAB and subsequently required bilateral carotid endarterectomies and a femoro-popliteal bypass two years later.

An examination of risk factors (Fig. 6) revealed smoking in 30 patients and a history of significant

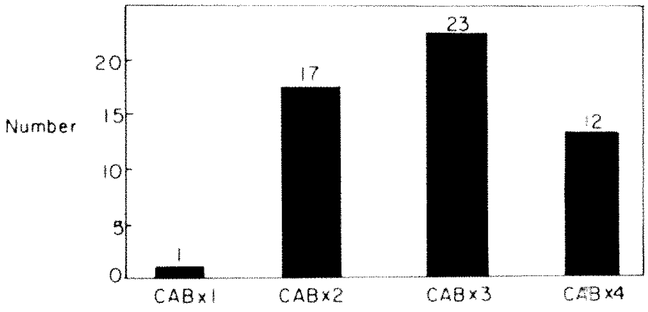


FIG. 2. Coronary revascularization.

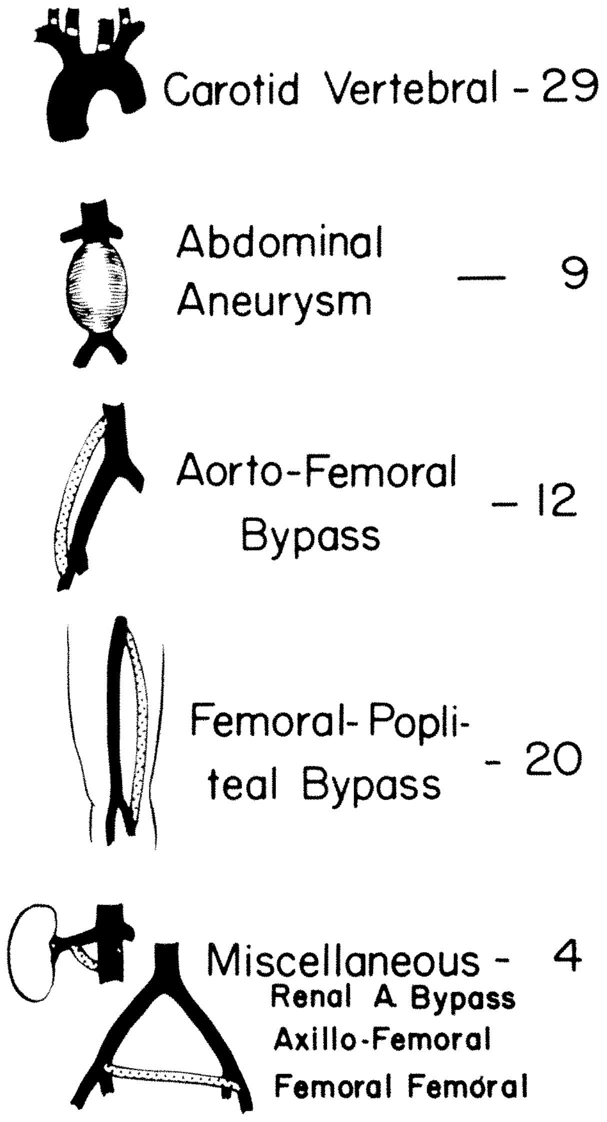


FIG. 4. Vascular procedure.

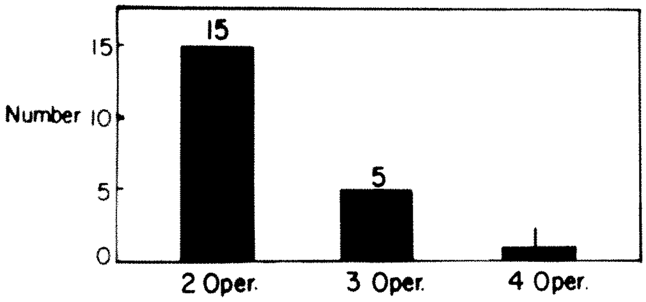


FIG. 5. Multiple procedures in 21 patients.

diastolic hypertension in 26. Diabetes was documented in only seven patients and a family history of cardiovascular disease in only 13. Elevated serum cholesterol was present in only six patients.

Results

Two deaths occurred in this series of 53 patients during the postoperative period. One was a 52-year-old man five years post-CAB with angina decubitus and cardiac cachexia. Six weeks prior to surgery, he developed severe peripheral ischemia with claudication after 100 feet, rest pain, and an ischemic ulcer of one foot. Angiographic evaluation revealed significant bilateral carotid disease (Fig. 7) in addition to bilateral superficial femoral occlusive disease. After a right carotid endarterectomy, a femoro-popliteal bypass was performed. On the fourth postoperative day the patient developed arrhythmias and cardiogenic shock. In spite of no acute ischemic changes on EKG, he developed ventricular fibrillation and expired 24 hours later.

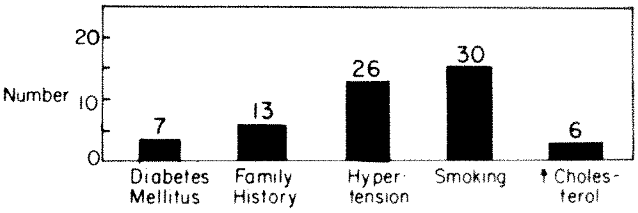


FIG. 6. Risk factors.

The second death occurred in a 64-year-old man in whom an axillo-femoral bypass was performed as an emergency on the day following CAB. The patient had had an aorto-femoral bypass 15 years previously which had been occluded for several years. There were no pulses palpable below the aortic level. During the period immediately following heart revascularization, it became evident that severe peripheral ischemia was present and restoration of distal flow was considered mandatory. Cardioversion for ventricular tachycardia was required on completion of the axillary-femoral-femoral bypass. The postoperative course was complicated by progressive renal failure, sepsis, ventricular arrhythmias and death four weeks following surgery.

Postoperative complications occurred in six patients (Table 1). Supraventricular arrhythmias developed in two patients while two patients developed pneumonia.

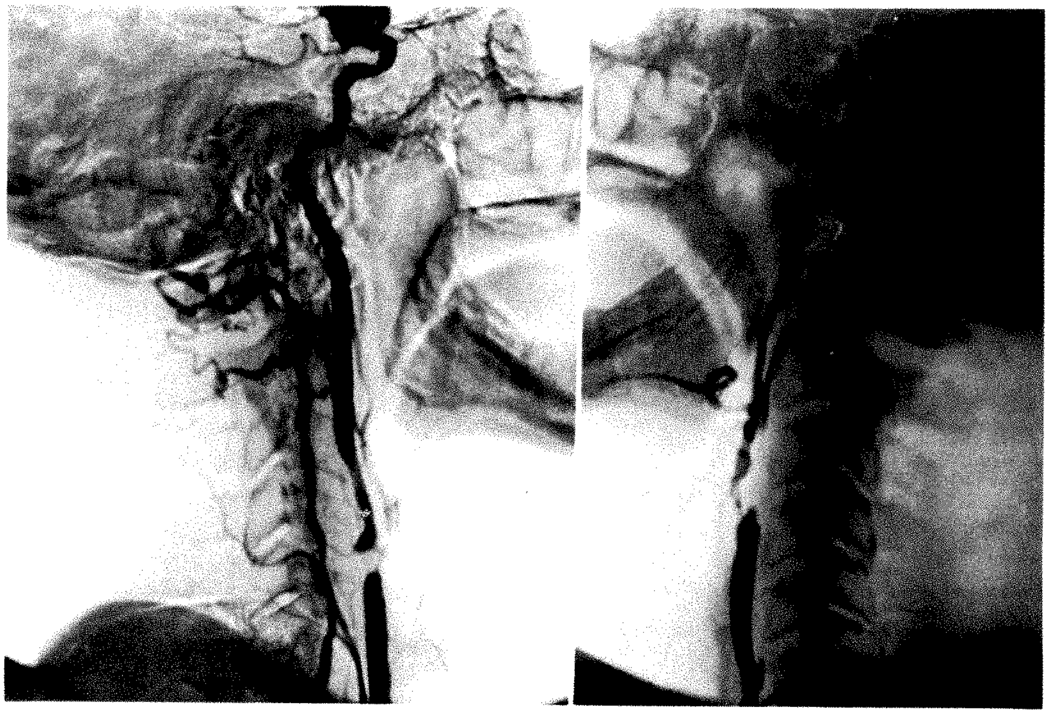


FIG. 7. Cerebral arteriograms revealed complete occlusion of the left internal carotid and significant stenosis of the right internal carotid.

TABLE 1. *Complications*

Type	Number
Arrythmias	5
(deaths)	(2)
Pneumonia	2
Wound infection	3
(loss of graft)	(1)

Wound infections occurred in two patients but were controlled with antibiotics and local care.

A final patient developed a deep wound infection around the Dacron® prosthesis of a femoro-popliteal bypass which necessitated removal of the prosthesis and subsequent amputation.

Three deaths have occurred in the follow-up period. The 48 surviving patients are all active, many carrying out their usual occupation with no restrictions.

The actuarial survival of these patients from the time of their CAB is shown in Figure 8. The projected survival of a normal group of similar age and sex falls within the 95% confidence limits for the study group showing an insignificant difference.

Discussion

Myocardial infarction has been a major cause for morbidity and mortality in patients requiring surgery. Mullins[4] found the operative mortality in patients with ischemic heart disease having major surgery to be 6.6%. Young, et al.[10] found that seven fatalities out of a series of 111 elective aneurysmectomies were due to myocardial infarction. The total postoperative cardiac morbidity in their series was 43%. CAB has proven effective in restoring blood flow to an ischemic myocardium and in relieving the symptoms of angina pectoris. Long-term follow-up of patients with CAB seems to show a reduction in the annual mortality without operation when compared to the projected mortality based on the severity of coronary artery involvement.[7]

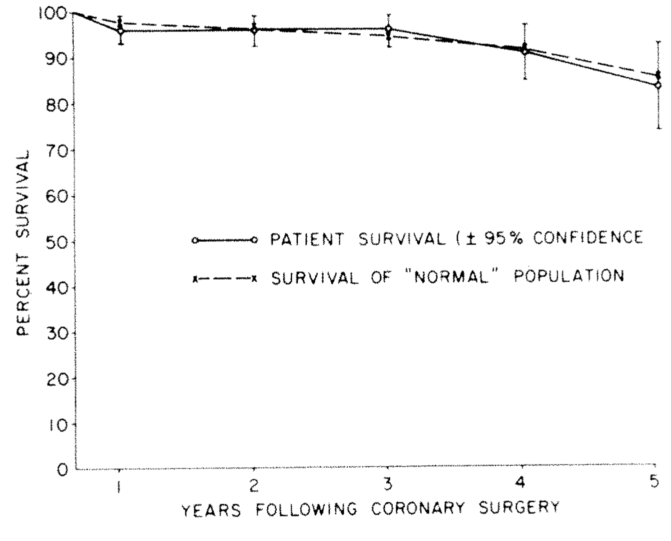


FIG. 8. Graph of predicted actuarial survival of patients in the study group (unbroken lines) versus time in years following CAB. Vertical bars show 95% confidence limits. The broken line represents the survival of a control group of "normal" subjects of similar age and sex (figures from Bureau of Vital Statistics).

The diagnosis and surgical management of carotid, abdominal, and peripheral vascular lesions has become relatively standardized. Coexistent lesions, however, present a dilemma in priority of surgical management. Rupture of an aortic abdominal aneurysm may follow carotid endarterectomy. Myocardial infarction also may occur as a complication of any surgical procedure, particularly with the potential for hypotension associated with vascular reconstructive surgery.

In an attempt to decrease the morbidity and mortality created by multiple organ system involvement by atherosclerosis the proper selection of sequential surgical procedures is critical. Simultaneous carotid endarterectomy and coronary bypass have been the two most frequently combined procedures.[1,5,6] The Cleveland Clinic results reported in 1976 for combined carotid endarterectomy and CAB indicated a higher morbidity and mortality than when selective sequential operations were performed.[8] Other collected series now seem to indicate, however, the relative safety of such an approach.[3] It would seem that further evaluation will be needed to determine the safest combination or sequence of surgical procedures.

In an attempt to define the risk of operation in a series of patients with previous myocardial revascularization, Scher and Tice[7] reviewed 24 operations in 20 patients from a larger group of 141 CABs. The one death occurred in a critically ill patient who required revascularization for impending gangrene of one lower extremity.

In our series of 53 patients, 22 major abdominal reconstructive vascular procedures were performed with no mortality or major morbidity. Our series illustrates, as do the series of McCollum[2] and Scher,[7] that with the increasing number of successful myocardial revascularizations patients will return with significant atherosclerotic lesions in other organ systems which will be treated best by vascular reconstruction. The data presently available suggest that patients who have undergone CAB are not only acceptable risks for subsequent emergency or elective vascular operations, but in fact may even have a lesser cardiac risk than the routine patient. Morbidity and mortality from cardiac causes may well be reduced by judicious evaluation of the entire cardiovascular system, followed by appropriately staged or combined cardiac and vascular procedures.

As further angiographic and epidemiologic data of coronary artery disease accumulate, peripheral vascular disease may be recognized as a marker for coronary artery disease, and we may arrive at the point of recommending coronary arteriography for selected patients with peripheral vascular disease as part of their preoperative assessment.

References

1. Bernhard, V. M., Johnson, W. D. and Peterson, J. J.: Carotid Artery Stenosis. Arch. Surg., 105:837, 1972.
2. McCollum, C. H., Garcia-Rinaldi, R., Graham, J. M. and DeBakey, M. E.: Myocardial Revascularization Prior to Subsequent Major Surgery in Patients with Coronary Artery Disease. Surg., 81:302, 1977.
3. Morris, G. C., Ennix, C. L., Lawrie, G. M., et al.: Management of Coexistent Carotid and Coronary Artery Occlusive Atherosclerosis. From the First Decade of Bypass Graft Surgery for Coronary Artery Disease, An International Symposium, Sept. 1977.
4. Mullins, C. B.: Selected Readings in General Surgery, #7, Vol. 4:1–39, 1977.
5. Okies, J. E., MacManus, Q. and Starr, A.: Myocardial revascularization and carotid endarterectomy: A combined approach. Ann. Thorac. Surg., 23:560, 1977.
6. Reis, R. L. and Hannah, H., III: Management of Patients with Severe, Coexistent Coronary Artery and Peripheral Vascular Disease. J. Thorac. Cardiovasc. Surg., 73:909, 1977.
7. Scher, K. S. and Tice, D. A.: Operative Risk in Patients with Previous Coronary Artery Bypass. Arch. Surg., 111:807, 1976.
8. Taylor, P. C.: The Results of Combined Myocardial Revascularization and Carotid Endarterectomy. Cleveland Clinic Foundation. Symposium, Coronary Artery Disease, Sept. 1976.
9. Tomatis, L. A., Fierens, E. E. and Verbrugge, G. P.: Evaluation of Surgical Risk in Peripheral Vascular Disease by Coronary Arteriography: A Series of 100 Cases. Surgery, 71: 429, 1972.
10. Young, A. E., Sandberg, G. W. and Couch, N. P.: The Reduction of Mortality of Abdominal Aortic Aneurysm Resection. Am. J. Surg., 134:585, 1977.

DISCUSSION

DR. GEORGE C. MORRIS, JR. (Houston, Texas): (Slide) Several months ago The Cleveland Clinic had a festival celebrating their ten years of coronary artery surgery. We were quietly celebrating our fourteenth; but at this festival we presented this work of Dr. Stanley Crawford, a member of this Society, Dr. James Howell, and my own cases. We analyzed a group of patients who had combined coronary and carotid arterial occlusive disease. We divided these 92 patients into three groups: those with simultaneous carotid and coronary reconstruction; those with the carotid being staged prior to the coronary revascularization; and a group staged with the coronary operation prior to the carotid reconstruction.

(Slide) We feel these results were illustrative of the point that the heart and mind must be treated together. There were six deaths in the group that had prior carotid reconstruction. All six deaths were related to acute postoperative myocardial ischemia. In the group that had simultaneous reconstruction, the mortality was only 4½%. In the group with prior coronary reconstruction there was one death, and this was the result of a stroke.

So this, we believe, teaches us that the coronary reconstruction should be done at the same time as the carotid reconstruction.

(Slide) At the present time, we are working on a study similar to Dr. Edwards', analyzing these secondary operations following prior coronary revascularization. This data will be presented at the Society of Thoracic Surgery meeting in January, 1978. As in his experience, the results are so surprising that they almost defied our own belief.

With 283 secondary vascular procedures, the mortality rate was about one percent. In 11 pulmonary resections, the mortality was zero. In 168 general surgical procedures, the mortality was 1.8%. And in 24 secondary reoperations for various reasons on the heart, mortality was only 4.1%.

Therefore, we have changed our technique of working up patients with prior coronary bypass. When they come in with secondary peripheral vascular problems, instead of doing separate percutaneous arteriograms, we enlist the help of some of our talented radiologists and let them do all these arterial studies by the catheter technique. But we make sure that during this study we also do an aortic root injection (our old-fashioned way of showing the coronary arteries prior to Mason Sones) to make sure that the bypass grafts are patent. If they are patent, you can do anything to the patient you want to with an extremely low mortality.

DR. WILLIAM E. WALKER (Closing discussion): We are grateful to Dr. Morris for his remarks, and are well aware of his large series of patients.

Our data have shown the protective effect of prior myocardial revascularisation on patients undergoing major vascular surgery, and that indeed coronary bypass returns even these patients with widespread vascular disease to a life expectancy not significantly different from normal.

A second important conclusion emerged from the study, however—that peripheral vascular disease signifies a highly increased risk of coronary occlusive disease, and in some instances, of itself, raises the question of coronary arteriography. Coronary artery surgery is at a crossroads. We have solved most of the evaluation and operative problems of these patients, and the major question now is: Whom best to study and revascularise? It seems likely that peripheral vascular disease may well be one of the best available markers for coronary artery disease. In most large series of major vascular reconstructions, approximately fifty percent of the patients die in the long-term follow-up period of ischemic heart disease and its complications.

In regard to the previous discussion about whether aortography is essential before abdominal aneurysmectomy, it seems that perhaps we should advocate not only an aortogram but also coronary arteriograms. The surgical payoff of coronary arteriography in our hospital is 33%, so one would only require a positive result in about a third of these patients to justify the study on general principles.

As many of you know, the senior author of this study, Dr. Edwards has had a coronary artery bypass, and as I watched him limp up the hill, jogging yesterday morning, I realised that the reason we embarked on this exercise was to figure out whether he should have his legs revascularised.

Further Evaluation of the Surgical Treatment of Obstructive Disease of the Left Main Coronary Artery

WILLIAM C. ALFORD, JR., M.D., HARRY L. PAGE, JR., M.D., GEORGE R. BURRUS, M.D.,
ROBERT A. FRIST, M.D., WILLIAM S. STONEY, M.D., CLARENCE S. THOMAS, JR., M.D.,
WILLIAM E. WALKER, M.D., PH.D.

From the Division of Thoracic and Cardiac Surgery,
St. Thomas Hospital and the Division of Cardio-Thoracic
Surgery, Vanderbilt University Medical Center,
Nashville, Tennessee

A protocol for the operative management of two patient groups with left main coronary artery disease has been evaluated. The period prior to and during induction of anesthesia is managed without using aortic balloon counterpulsation. Of the 86 patients undergoing coronary artery bypass for left main coronary artery disease from 1970 to 1973, there was a surgical mortality of 8.1%. Follow-up of the survivors from 48 to 87 months revealed three coronary and five non-coronary related deaths with survival to seven years of 75.6 ± 5%. If the operative mortality is excluded, there is an observed survival to seven years of 82.4 ± 4.8%, almost the same as a "normal" population of similar age and sex. Utilizing the same protocol, 90 similar patients undergoing coronary artery bypass in 1976 had an operative mortality of 4.4%. The deaths were not related to induction of anesthesia. The perioperative infarction rate (2%) and postoperative cardiac enzyme determinations were no greater in a random group having the same operation for less severe forms of coronary artery disease during the same time period. This method of management for patients with significant left main coronary artery disease is judged superior to other more complex techniques.

SIGNIFICANT OBSTRUCTION of the main left coronary artery produces a level of myocardial ischemia which makes medical management unappealing. Conversely, the surgical treatment of this degree of ischemia by coronary artery bypass should result in a significant improvement of survival within such a group, especially if a reliable means of operative protection of the myocardium can be achieved. However, initial reports of myocardial revascularization in such patients revealed unacceptable mortality rates when compared to other forms of this disease. In searching for ways to lower this risk, we have concentrated our efforts in refining techniques applicable to all forms of coronary artery disease rather than evolve separate ones for left main lesions. In light of recent reports suggesting the necessity for routine intra-aortic balloon counterpulsation prior to operating on patients with left main coronary artery disease,[3,4] a review of our alternate approach to this problem seems warranted.

Two groups of patients undergoing coronary artery bypass (CAB) for greater than 50% stenosis of the left main coronary artery at St. Thomas Hospital were reviewed. The first group consists of 86 patients operated on between 1970–1973 and followed through May, 1977. The results were used to determine the long-term effectiveness of this surgical approach to the problem. A second group of 90 patients operated upon in 1976 in a similar manner was reviewed to attempt to validate the lack of need of balloon support in this patient population.

Clinical Materials and Management

Eighty-six patients were operated on between February, 1970 and June, 1973. The method of managing these patients has been reported previously.[1] There were seven operative deaths representing an 8.1% mortality rate. All 79 survivors have been followed through periods ranging from 48 to 87 months and the results tabulated on an actuarial basis.

Ninety-two patients with left main coronary artery stenosis were operated on in 1976 following the same protocol. Briefly stated, the operation is done urgently but not as an emergency procedure. Enemas are omitted as part of the preoperative routine. Drugs that have contributed to a stable cardiovascular state are continued to the time of operation. Premedication consists primarily of tranquilizers with little or no narcotics. Arterial pressure monitoring is established with

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

Reprint requests: William C. Alford, Jr., M.D., St. Thomas Medical Building, Suite 501, 4230 Harding Road, Nashville, Tennessee 37205.

0003-4932-78-0600-0658-0085 © J. B. Lippincott Company

a local anesthetic while oxygen is administered by face mask. Induction of anesthesia is accomplished slowly with the intravenous agent deemed appropriate for the observed blood pressure and pulse. Vasopressors, inotropic agents, vasodilators and antiarrhythmic drugs are immediately available and used as needed. The operation is then done in a routine manner with generalized hypothermia to 32° and intermittent aortic cross clamping for distal coronary anastomoses. Two or more grafts are constructed per patient utilizing saphenous veins and mammary arteries as indicated.

Results

Of the originally reported 86 patients with left main coronary artery stenosis, there were seven operative deaths and eight late deaths. Three of the late deaths resulted from acute myocardial infarctions, while five were unrelated to the coronary circulation. Three of the current survivors have had a second coronary artery bypass operation three, ten and 48 months after the initial procedure. Seventy-one of the original groups of 86 are currently alive. This is illustrated in Figure 1 on a life table where only the operative survivors are included. This is compared to a "normal" population of similar age and sex (figures from Bureau of Vital Statistics). Predicted normal survival falls within the 95% confidence limits for the study group showing no significant difference. Three survivors have reportable but stable angina and two others have experienced nonfatal myocardial infarctions. Three have undergone other major vascular operations, three have had cerebrovascular accidents and two report moderate claudication.

Results of the 1976 Group

In 1976, 105 of 2700 patients undergoing coronary angiography at this institution were judged to have greater than 50% stenosis of the left main coronary artery. Thirteen were advised or elected not to undergo coronary artery bypass and six of those have subsequently expired. The remaining 92 patients received coronary artery bypass grafts. The average age was 58.3 years, 3.3 years greater than in 1973. Twelve of the 92 or 13% were women, which is 3.4% greater than the first study. The degree of narrowing of the main left coronary artery was calculated at 50–65% in 31 patients, 70–80% in 33 patients, 85–95% or greater in 24 patients and 100% occlusion in four patients. The number of grafts performed per patient is shown in Table 1, as is the use of the internal mammary artery for graft material.

Two of the 92 were brought to the operating room in ventricular fibrillation. Although one of these survived intact, only the remaining 90 were influenced by the protocol previously outlined. Four of these 90 were postoperative deaths (4.4%). In retrospect, the use of preoperative balloon counterpulsation apparently would not have benefited any of them (Table 2).

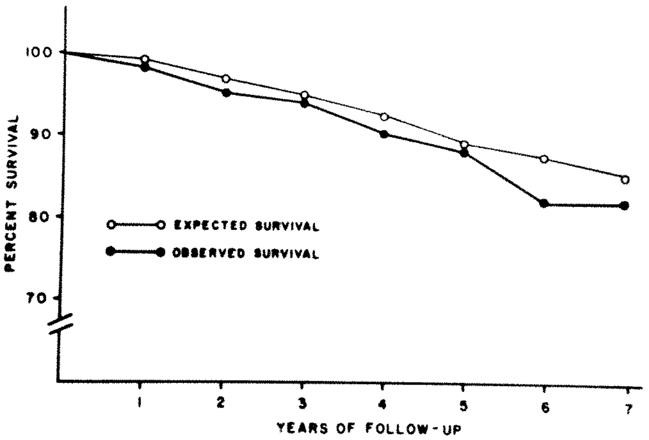


FIG. 1. Survival of 79 operative survivors of left main coronary artery disease, from 1970–1973 group, with superimposed survival curve for sex- and age-matched group from normal population.

It was also determined that myocardial damage in the 86 survivors was no greater than in a random sampling of one hundred patients undergoing CAB for reasons other than left main coronary artery disease during the same time. Two patients in the left main group had new Q waves appear in the postoperative electrocardiograms, but neither had significantly elevated cardiac enzyme determinations. Six patients in the random control group demonstrated new Q waves postoperatively and three of these had elevated enzyme levels as well. A comparison of the postoperative cardiac enzyme determinations of all patients in these two groups reveals no significant difference (Fig. 2). Consequently, no indication for use of preoperative balloon counterpulsation can be made based on these data.

TABLE 1. *Left Main Coronary Stenosis 1976—Grafts Performed*

Coronary Artery Bypass	Number of Patients
x1	0
x2	13
x3	46
x4	28
x5	4
x6	1
	Total = 92
Single mammary artery used	60
Double mammary artery used	13
	Total = 73

TABLE 2. *Left Main Coronary Artery Stenosis Operative Deaths, 1976*

Patient	Age	Sex	Operation	Cause of Death	Post-operative Day
E. W.	67	M	CAB* × 3, excision carcinoma left lung	Multiple vessel thrombosis, metastatic carcinoma lung	16
H. S.	63	M	CAB* × 5	Stroke; femoral artery and probable cerebral embolus	16
R. M.	71	M	CAB* × 2	Thrombosis of aorta, thrombosis of axillo-bifemoral graft	41
F. G.	47	M	CAB* × 4	Myocardial infarction resulting from thrombosed coronary artery aneurysm	1

* CAB = Coronary artery bypass.

Discussion

In peripheral arteries, a 50% reduction in the luminal diameter is equivalent to a 75% reduction in cross sectional area and begins to produce a significant reduction of blood flow.[6] The clinical course of patients with such a lesion involving the left main coronary artery treated medically has been documented for periods up to ten years following coronary angiography.[2,5,10] A yearly mortality of 10% or more is reported. At greatest risk are those patients with diffuse artery disease,[5] decreased left ventricular function,[10] and lack of coronary collateral circulation.[11] The randomized study of patients by the Veterans Administration of stable angina and left main coronary artery disease showed a three year survival of 60% in the medically treated group.[10] Conversely, numerous reported series of patients surviving coronary artery bypass for left main coronary artery disease from two to four years, including the randomized VA study, have shown a longevity figure similar to ours.[2,7,8,10,11] Some of these results are summarized in Figure 3.

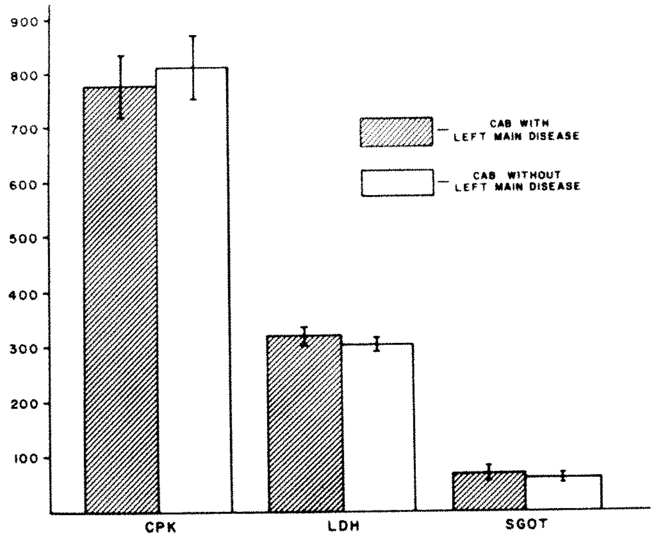


FIG. 2. Comparison of postoperative enzyme determination between the 1976 study group had a similar random cohort without left main disease.

These data strongly support the idea that coronary artery bypass improves the chance of survival of patients with left main coronary artery disease in spite of the tendency of the underlying disease to be progressive. Although admittedly a selected subset, these results should have some meaning to other patients with significant coronary artery disease having the same operation.

The features of this severe form of coronary artery disease that make it the most lethal also make it the most challenging. If these people can be identified, investigated and successfully undergo coronary artery bypass, the observed survival is dramatically improved. The conduct of the operation has been a major concern of our group from the earliest attempts. We conclude that modification of anesthetic induction applicable to any critically ill patient will avoid ventricular fibrillation and cardiac arrest and allow a smooth operation. If indicated, one or two mammary arteries can be dissected and as many bypass grafts constructed as needed. No evidence of cardiac damage or alteration in the postoperative course has been found compared to randomly selected patients having the same operation for less severe disease. Considering the expense and rate of complications,[11] intra-aortic balloon counterpulsation has not been used routinely, but rather for refractory cardiogenic shock and inability to wean patients from the pump.

The fact that four of 90 patients managed in 1976 in the manner described above were postoperative deaths deserves comment. A review of their operative notes confirms that there was no difficulty with induction of anesthesia or conduct of the operation. Each had a thrombotic complication unrelated to hypotension and some undefined hypercoagulable state may have been contributory.

In summary, obstructive disease of the left main coronary artery constitutes a management problem of considerable magnitude. Medical treatment is unsatisfactory and coronary artery surgery may be hazardous. Follow-up studies extending more than seven years demonstrate the beneficial results of coronary artery bypass in patients with this lesion.

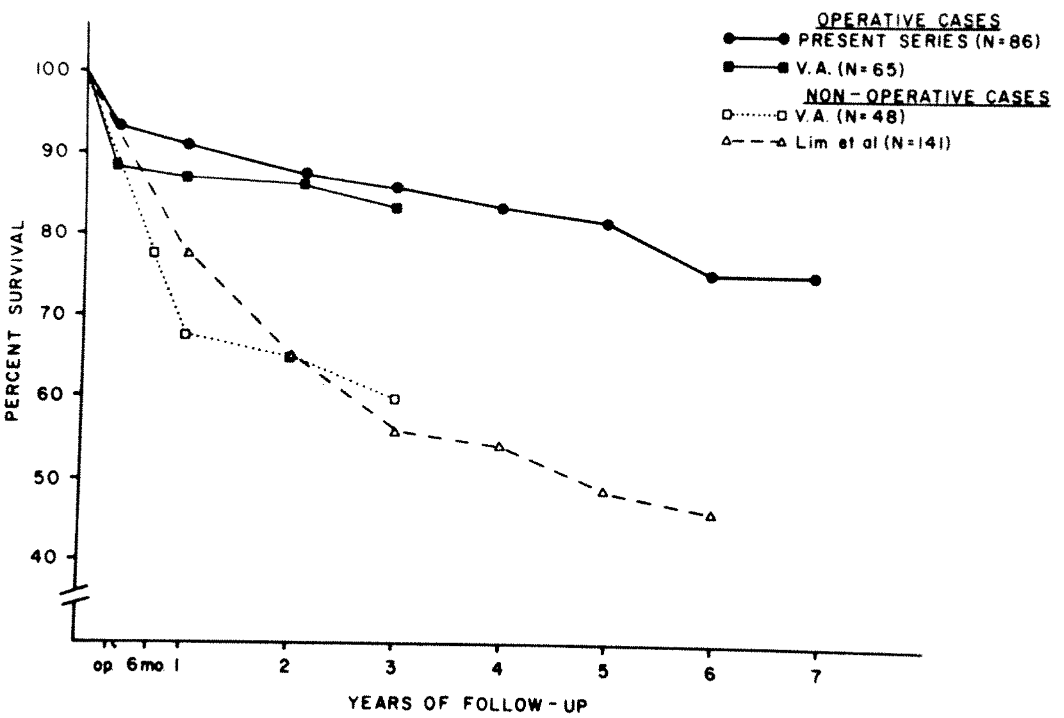


FIG. 3. Actuarial follow-up of 1970–1973 study group superimposed with other operative and non-operative groups for comparison.

References

1. Alford, W. C., Jr., Shaker, I. J., Thomas, C. S., Jr., Stoney, W. S., Burrus, G. R. and Page, H. L.: Aortocoronary Bypass in the Treatment of Left Main Coronary Artery Stenosis. Ann. Thorac. Surg., 17:247, 1974.
2. Cohen, M. V., and Gorlin, R.: Main Left Coronary Disease—Clinical Experience from 1964–1974. Circulation, 52:275, 1975.
3. Cooper, G. N., Jr., Singh, A. K., Christian, F. C., Cashman, C., Vargas, L. and Karlson, K. E.: Preoperative Intra-aortic Balloon Support in Surgery for Left Main Coronary Stenosis. Ann. Surg., 185:242, 1977.
4. Garcia, J. M., Mispireta, L. A., Smyth, N. P. D., Keshishian, J. M., Marsh, H. B. and Bacos, J. M.: Surgical Management of Life-threatening Coronary Artery Disease. J. Thorac. Cardiovasc. Surg., 72:593, 1976.
5. Lim, J. S., Proudfit, W. L. and Sones, F. M.: Left Main Coronary Arterial Obstruction: Long-term Follow-up of 141 Nonsurgical Cases. Am. J. Cardiol., 36:131, 1975.
6. May, A. G., DeWeese, T. A., and Rob, C. G.: Hemodynamic Effects of Arterial Stenosis. Surgery, 53:513, 1963.
7. Mehta, J., Hamby, R. I., Hoffman, I., Hartstein, M. L. and Wisoff, B. G.: Medical-Surgical Aspects of Left Main Coronary Artery Disease. J. Thorac. Cardiovasc. Surg., 71:137, 1976.
8. McConahay, D. R., Killen, D. A., McCallister, B. D., Arnold, M., Reed, W. A., Crockett, J. E., and Bell, H. H.: Coronary Artery Bypass Surgery for Left Main Coronary Artery Disease. Am. J. Cardiol., 37:885, 1976.
9. Pace, P. D., Tilney, N. L., Lesch, M. and Couch, N. P.: Peripheral Arterial Complication of Intra-aortic Balloon Counterpulsation. Surgery, 82:685, 1977.
10. Takaro, T., Hultgren, H. N., Lipton, M. J. and Detre, K. M.: The VA Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease. II. Subgroup with Significant Left Main Lesions. Circulation, 54:107 (Suppl. III), 1976.
11. Talano, J. V., Scanlon, P. J., Meadows, W. R., Kahn, M., Pifarre, R. and Gunnar, R. M.: Influence of Surgery on Survival in 145 Patients with Left Main Coronary Artery Disease. Circulation, 51 and 52:105 (Suppl. I), 1975.

DISCUSSION

DR. DUNCAN A. KILLEN (Kansas City, Missouri): I would like to comment relative to each paper. I would like to show data that I think confirm the data that the authors have presented, and our conclusions, I think, are very similar.

(Slide) This relates to the treatment of patients with left main coronary artery occlusions, or partial occlusions. At the St. Luke's Hospital in Kansas City we have treated 270 such patients from 1971 through 1976, and this represents approximately 10% of our experience with isolated coronary artery bypass patients. We have followed these patients, and these are the number of patients alive at follow-up. As you see, beyond three years we really do not have a very large group of patients followed, but the survival curve—and this includes the operative mortality—at five years is 92%. And as mentioned earlier, this is comparable to the survival of the average U. S. citizen matched for age and sex. I think this is something that is very important. Otherwise, patients selected for operation (and admittedly, all patients are not operated on) have a survival which is equivalent to that of the average population.

Now, if you look at the medically treated group, we go back to the series reported a long time ago from the Cleveland Clinic, showing the overall survival of patients with similar lesions, and this curve represents the VA study which has been referred to earlier. These patients are from a randomized study. Otherwise, these patients are candidates for surgery, and were not operated on. And I believe that from the data that we have heard presented this morning we have seen enough randomized studies of left main lesions. I think it's clear that surgery is indicated in this group, and I think that is becoming general opinion in the cardiologists' minds as well.

(Slide) I would like to speak to the long-term follow-up of all patients with coronary artery disease undergoing operation. We have recently followed up 282 patients that were operated on at least five years previously, and we were able to get follow-up on all of these patients to the time of death or for at least five years. We have surveyed them according to the course of their angina, and as you can see, there has been deterioration in their angina status, and at five years only 57% remain angina free. And I think this is what we would anticipate. Coronary artery disease is a progressive disease. They have certainly not reverted to their preoperative status, but there is deterioration, and, of course, some of these patients have required reoperation during this period of time.

(Slide) And the last slide that I would like to show is the survival of these initial 282 patients; and again, this includes the operative mortality. And at five years the patient survival was 86.9% and above it is the survival of the average population, matched for age and sex. Approximately 60% of these patients had three vessel disease. We have since, of course, extended this series, and extended the follow-up. In the follow-up of the first 2000 patients operated on 1971 through 1976, we have found that the survival curve has shifted upward somewhat, and the projected survival, using the life table method, is 90%, which is equivalent, essentially, to the population, when matched for sex and age.

Dr. Thomas L. Kilgore, Jr. (Jackson, Mississippi): Drs. Morris and Lawrie's presentation is in rebuttal to the widely publicized VA report with which you are all familiar. I would like to present some observations on a group of 321 of our patients having coronary surgery and followed for a mean of four years, in hopes of emphasizing the conclusions that Drs. Lawrie and Morris have presented.

(Slide) These few slides compare the actuarial survival curves of our surgical series, shown in yellow, with that of a group of patients receiving medical therapy alone, as previously reported by Dr. Joseph Reeves and associates, shown in orange. Cardiac as well as noncardiac late deaths were included in both the surgical and medical series. Operative deaths also entered these curves.

Forty-eight per cent of our 321 patients received two grafts, though some had other vessels that were diseased but not bypassable. We observed a 3% annual mortality, compared to the 7% rate seen in the medical series with two vessel disease.

Thirty-eight per cent of the series received three or more grafts, and the annual mortality was 2%, while the medical series of three vessel disease died at a rate of 12% per year.

In the overall surgical series, the operative mortality was 2.4%, and the survival at four years was just under 90%, whereas only about 82% of the medical series were alive at the end of two years.

I would point out that the VA study excluded those patients with unstable angina, while patients with that syndrome were included in both the medical and surgical series shown here.

The authors' observations present convincing arguments in favor of the superiority of surgical management versus medical therapy alone, and my own experience leads me to agree with their conclusions.

In closing, I would like to ask Dr. Morris if any patients in his series have had recurrence of angina after initial improvement; and if so, what percentage of them were considered as candidates for reoperation?

Dr. Charles R. Hatcher, Jr. (Atlanta, Georgia): I think that Dr. Morris' paper is exactly the type of data that is required to put the medical/surgical therapy controversy, based on the VA cooperative study, in proper perspective.

I especially wish to emphasize our agreement with the conclusions that the determinants of survival are essentially two: the status of ventricular function preoperatively, and the quality of the surgery.

The quality of the surgery, of course, can be easily defined through the parameters of operative mortality, vein patency rate, perioperative infarction rate, and completeness of revascularization.

It is a bit unfortunate that just at the time that the quality of surgery has reached such a pinnacle of success, the value of the operation should be brought into question. I realize that the VA researchers did not mean this to occur, but they took a very limited group of patients with excellent ventricular function, at minimum risk, and then compared the short-term survival rates of the medical versus the surgical group. The lay press and others have taken that basic comment and extrapolated it to cover many subsets of coronary artery disease.

I would like to make the plea that at the present time, based on the fact that we have figures such as Dr. Morris' to give us the confidence that the long-term survival is going to be excellent, and with data accumulating showing that the quality of surgery is outstanding, we continue to expand the role of surgery in the treatment of coronary artery disease.

(Slide) Before leaving Atlanta, I pulled from our computerized data collection system the last 1000 patients operated upon for coronary artery disease with bypass surgery. This represented a 15 month experience, and during that time the hospital mortality was 1%, and the perioperative infarction rate 5%. The graft patency rate of 90% is based on those restudies performed over the last three years. These results are quite typical of the results that are being achieved by members of this Association in many surgical centers.

(Slide) To comment on left main disease, I would say that there is no question in anyone's mind at the present time that left main disease should be treated surgically rather than medically. This is a short follow-up, to be sure, but in 180 patients seen with left main disease at Emory, 138 were operated upon, and 24 months later 85% were alive, whereas the medical service, in not operating on 47, had a mortality of 43%.

Similarly, if we limit our application of surgery to severe obstruction and/or significant left ventricular dysfunction, as defined here by ejection fractions below 35 and LVEDP's greater than 20, or take a group in whom both the LAD and the right coronary artery were totally occluded, we find that even there the operative mortality is quite low, and that the follow-up is quite satisfactory.

Even in advanced disease, realizing that these patients will not have the good outlook of those with excellent ventricular function, the results are sufficiently good to warrant application of surgery without question.

And, finally, those patients who have not had a satisfactory course following acute myocardial infarction may on occasion be operated upon with dramatic benefit. We recently reviewed a group of 35 patients operated upon and divided into these groups, ten operated on within 24 hours of acute myocardial infarction, nine within two to seven days of acute myocardial infarction, and 16 patients operated on from eight days to one month of acute myocardial infarction. These are patients who had certain complications that required surgical intervention.

The hospital mortality was 0 in that group of 35 patients, and we have lost none to follow-up, albeit the follow-up is quite short. 68% were completely relieved of angina, 26% improved, and 6% were either unchanged or worse. Seventeen of those 35 patients have been restudied for graft patency. In that group all grafts were present in 76%.

Dr. Frank C. Spencer (New York, New York): (Slide) First, I want to emphasize two basic facts about coronary disease, which I briefly alluded to on Monday. It causes about 600,000 deaths in this country annually. This large number accounts for more than one-half of all deaths in the American male each year from all causes combined. This alarmingly high figure itself, which has been true for many years, automatically raises serious questions about the efficacy of non-operation therapy in many patients because most of the present forms of medical therapy have been available for the last 10–20 years.

The second point not widely appreciated is that to date, only two factors have been proved to influence the death rate: avoiding cigarette smoking and controlling hypertension. Other forms of medical therapy, including limitation of lipid intake, betablockers, weight reductions, and jogging, are all reasonable but are actually even more unproven on influencing coronary disease than coronary bypass. Hence, the debate about the indications for coronary bypass is not one of comparing a proved form of therapy with a new form of surgical therapy, but the more basic one of proving the benefit of both forms of therapy presently employed.

(Slide) One reason for the confusion in data is the wide variability in atherosclerosis, ranging from the very mild to the very lethal. This variation in itself is due to the interplay of two opposing factors: How rapidly the disease progresses versus how rapidly the collaterals develop. Unfortunately, at the present, our efforts are very limited in influencing either one of these two processes, progression of atherosclerosis or growth of collateral circulation. Hence, there is a very wide spectrum in coronary disease and the importance in all studies is to compare comparable groups.

The disease is similar to atherosclerosis in the femoral artery. Few would advocate bypass grafting whose only symptom was claudication after walking eight to ten blocks, for abundant data indicate that the risk of gangrene within five years is very small. By contrast, no one would argue about bypass grafting for someone with rest pain, dependent rubor, and early ulceration, where amputation will surely become necessary unless operation is done.

(Slide) Our data from New York University were presented at the Toronto Meeting of the American Association for Thoracic Surgery last April. A 98% follow-up of our total experiences at New York University with elective bypass operations, including over 1100 patients over a period of about seven years, found that 88% were alive five years later.

In analyzing this slide in detail, the overall mortality for the five year period was 5%, decreasing to the range of about 2% in the last few years. For the overall group of each 100 patients operated upon, 95 left the hospital. Five years later, 88 were alive, with seven dying during the period of five years, an average annual mortality of only 1.4%.

A second surprising point from this actuarial curve is that the slope of the curve is even. One would predict that if the grafts closed, or the atherosclerosis progressed rapidly, the curve should progressively change with an increasing mortality rate three to five years later. A second important point is that the slope of this actuarial survival curve exactly parallels that for a similar matched population of age and sex, indicating that operation had a very strong beneficial influence on longevity. Not mentioned, this is even more remarkable because the majority of these patients were seriously disabled with their disease and were operated upon after attempts at all available medical therapy had failed.

(Slide) This slide shows similar figures from the Ochsner Clinic, given at one of our national vascular meetings last summer in Rochester, New York, showing a five year survival near 90% in a series of about 1000 patients.

The similarity of our results and those from the Ochsner Clinic with the results reported by Drs. Morris and Lawrie is striking. I would like to emphasize several points.

First, 670 of their patients have been followed for over five years and angiograms performed on 105 of these. At five years, the vein graft patency rate was 89% and over 96% had one patent graft. To my knowledge, these are the best long-term data about graft patency ever published. Hence, one of the major questions about coronary bypass answered in this study is that patency for at least 5 years of the vein grafts is probably in the majority of patients.

Their survival rate ranges 81–92%, varying with ventricular function, a factor well known to have a strong influence on longevity. I had the opportunity of reading the manuscript in detail and would recommend its close study by all working in this area.

In closing, I have several questions: 1) What are your current indications for operation, severity of angina or the degree of obstruction on the angiogram? More specifically, would you recommend bypass on a patient with asymptomatic triple vessel disease on the angiogram? 2) What is your present technique of bypass, has it been modified with experience, and what is the frequency of myocardial infarction following bypass? 3) Finally, with the great concern about cost of medical care, what percentage of your patients are working?

Dr. Gilbert S. Campbell (Little Rock, Arkansas): Cruelty to animals is abhorrent to most of us. In the discussion thus far the Veterans Administration Trial (randomized prospective study on the treatment of a well defined group of patients with coronary artery disease) has been kicked around like a rejected mongrel dog. Perhaps some kicks are deserved, but all the kickers may not be flawless in their clairvoyance.

Dr. Timothy Takaro headed the surgical section of the Veterans Administration study. I am pleased that the Little Rock VA Hospital put more patients into the study than any other hospital. The surgical procedures were done by Drs. Raymond C. Read and G. Doyne Williams. The quality of the surgery was not contaminated by my expertise so I can speak objectively.

The VA study has evoked a visceral rather than a cerebral response in many surgeons and cardiologists. The VA Trial may or may not tarnish the golden egg of coronary artery surgery but at least some have asked "Is it solid gold?"

I'm not questioning the beautiful papers presented here, but I do know that in some locations if a person has a little dyspepsia and grabs his chest, he may have a skip graft. Now if that doesn't help him, he may be subjected to a careful history and physical examination.

Dr. Frank Spencer's comments were right to the point. Lipid lowering has been proven ineffective to date with diet and/or drugs. The best handle to date on lipid lowering is a surgical handle—distal ileal bypass described by Drs. Henry Buchwald and Richard Varco. At the University of Arkansas, we're a very small part of a scientific, prospective, randomized study on the surgical control of hyperlipidemia. It is hoped that in the years ahead we will have 1000 patients, 500 randomized to the ileal bypass (which drops lipids 40–45%) and 500 control patients. It's the only operation that I'm aware of that gets at the metabolic cause of atherosclerosis.

A major league ball player with coronary artery occlusion did not have a skip graft but had the distal ileum (the distal one third) bypassed by Dr. Buchwald at the University of Minnesota. Subsequent arteriography showed some resolution of the obstructive lesions in the coronary arteries. It is the only operation that attacks what may very well be the cause of these lesions and hopefully the Minnesota based study will provide a definitive answer to the lipid-atherosclerosis hypothesis.

Dr. William C. Alford, Jr. (Closing discussion): I am indebted to Dr. Killen for presenting his figures, primarily because his results are better than ours. I believe they have the lowest operative mortality and best long-term follow-up of any group that I know of, and I'm trying to do as well.

We think this study has shown that in the left main group—which even Dr. Campbell doesn't question—coronary artery bypass is effective in increasing survival over the non-operated group. The operation was not designed for that, as you know. It was designed to relieve angina, and, as Dr. Hatcher has shown, it is most effective in that particular aspect.

However, if coronary bypass for left main coronary disease can be accepted as increasing survival, then perhaps it should be looked at more critically in all significantly ill patients with the same disease.

Dr. Gerald M. Lawrie (Closing discussion):

I must say, I feel something like a fox let loose in a henhouse, after all these discussions, with so many things to answer. Perhaps if I could show some slides to give the perspective from which our current attitudes have developed.

(Slide) We are conducting an on-going follow-up of a large group of patients, all operated on more than five years ago. Because we have had the opportunity to review all the patients more than five years after operation, the actuarial technique of analysis becomes redundant, because every patient has been followed through the entire interval of five years.

This is a consecutive series of 1108 patients operated on by Dr. Morris and Dr. Howell at Baylor College of Medicine between 1971 and 1972. It includes left main disease, and includes patients with impaired left ventricular function including those who had left ventricular aneurysmectomy.

No patient has been excluded because of poor ventricular function. And, in fact, at that time there was considerable interest in surgery for congestive heart failure, so a number of patients had quite severe congestive heart failure.

The overall survival in this group, operated between 1971 and 1972, was 90.7%. This is far superior to the medical and surgical results of the VA Cooperative study, which was a far more highly selected group of patients. Our results now are superior to these particularly in relation to operative mortality and the degree of revascularization achieved.

A curve of survival for a normal population was prepared for us by the actuarial director of Prudential Insurance Company from the age and sex of every one of these patients—it is an exact matched curve. The normal survival was 92.7%.

If we look now at patients with an end diastolic pressure of less than 15 mm of mercury, and no discrete akinetic or aneurysmal area of left ventricle (and we define these patients as having good left ventricular function; not normal, because many of these had dilated ventricles and impaired ejection fractions, but we did not use this to classify them) simply these two objective parameters.

We can see that the survival in this group of patients is actually superior to normal beyond five years; and once again, superior to the VA study.

Now, looking at the survival of the various subgroups in more detail, the unbroken lines are the patients with good left ventricular function, and the broken lines, are the patients with poor ventricular function, as we have defined these terms.

It is apparent that successful revascularization has eliminated the difference in survival of patients beyond five years regardless of the preoperative extent of their coronary artery disease. In other words, all these patients, including single, double, triple and left main disease, have ended up with comparable survival, and all those patients with good left ventricular function have normal survival.

In other words, we feel that a functioning bypass does, in effect, eliminate the significance of a coronary artery lesion. In a recently published study, we examined graft function and progression of disease in considerable detail. It is not accurate to say that coronary artery disease is a relentlessly progressive disease. Less than 10% of these patients had significant progression over a five year period.

Coronary artery disease, like atherosclerosis elsewhere in the body, by and large, progresses at a slow rate. Of course, we do see a small number of patients with rapidly progressive disease, but by and large it is stable over five years.

Looking at the patients with poor ventricular function, their survival is far superior to any group of similar medically treated patients. And now we have found the reason why: since we have introduced the radioisotope ejection fraction studies (which have become available recently), it has become apparent that what we suspected clinically for many years but couldn't show—that coronary bypass improves ventricular function—is absolutely correct.

And we have now extended this even into the group of patients with poor ventricular function without angina. In selected patients, we have shown doubling of the ejection fraction postoperatively by radioisotope study. So the improved survival here can be attributed to revascularization of the impaired ventricle.

Of course, some of this impairment is irreversible, and so these people continue to have a depressed survival.

As we have continued to follow these patients, we have employed professional police investigators to pursue people to the ends of the earth, and we have now been able to obtain an almost 99% follow-up beyond five years.

We believe, therefore, that there is no question but that the coronary bypass operation restores people with good preoperative left ventricular function to normal, not improved, but normal life expectance. And we believe this has extremely important implications in the management of coronary artery disease.

We feel coronary disease is analogous to a malignancy. We're dealing with a malignant disease that will take life, and we can no longer tolerate patients being allowed to deteriorate into a state of ventricular function where surgery can no longer offer them the opportunity which they deserve to achieve a normal life expectancy. And I think this is something about which we need to educate our cardiological colleagues.

The other thing is, there is no need for any form of randomized prospective study in regard to normal ventricular function. What we now need is a medical series of angiographically similar patients who have achieved a normal five-year survival; and I sincerely doubt that this will be forthcoming.

I think, in answer to Dr. Campbell, none of us object to scientific endeavor, and I think all of us accept the VA Co-operative study as a very honest attempt to answer a difficult question. My own objection to it is the rather slanted editorial which accompanies the article, and which was communicated to the press in rather an exuberant fashion, and which has led to so much suffering among so many patients.

The other point which I think bears emphasis is that the claim in the body of the report itself that the quality of surgery achieved in the VA cooperative study was acceptable for 1972–1974 is just not acceptable. Neither the operative mortality in such a good-risk group of patients nor the graft patency achieved even approached that being achieved by many large centers prior to 1972, as we have demonstrated.

In answer to Dr. Kilgore, we have had to reoperate on a small number of patients. The most common reason has been an inadequate initial operation. And as you saw in our presentation, a number of patients between 1968 to 1971 had too few grafts placed. Also, when we reviewed some of the early arteriograms, we found that we had been underinterpreting disease quite consistently at that time. So the most common reason has been either unoperated lesions which were there all the time or lesions which have progressed, and, infrequently, graft occlusion.

We have been very interested in the grafts, and we have studied them both angiographically and histologically beyond five years. We have reported in some detail on the role of intimal proliferation in graft patency and we have published another article on graft atherosclerosis, which is rarely of significance.

In answer to Dr. Spencer, we did not exclude patients with hypertension. We did list the exclusions of the VA study. I'm sorry we didn't get the manuscript to you sooner, but the federal government has been taking an active role in inhibiting coronary bypass, and we suspect the U.S. Postal Service has been enlisted to further this end.

Now, as to indications for operation, angina pectoris remains our principal indication for investigation. Since we have obtained the results of these long term studies we have become more aggressive in offering operation to people with double and triple vessel disease, as well as left main disease, on the basis of anatomy alone: because our data tells us that these people can be restored to a normal life expectancy.

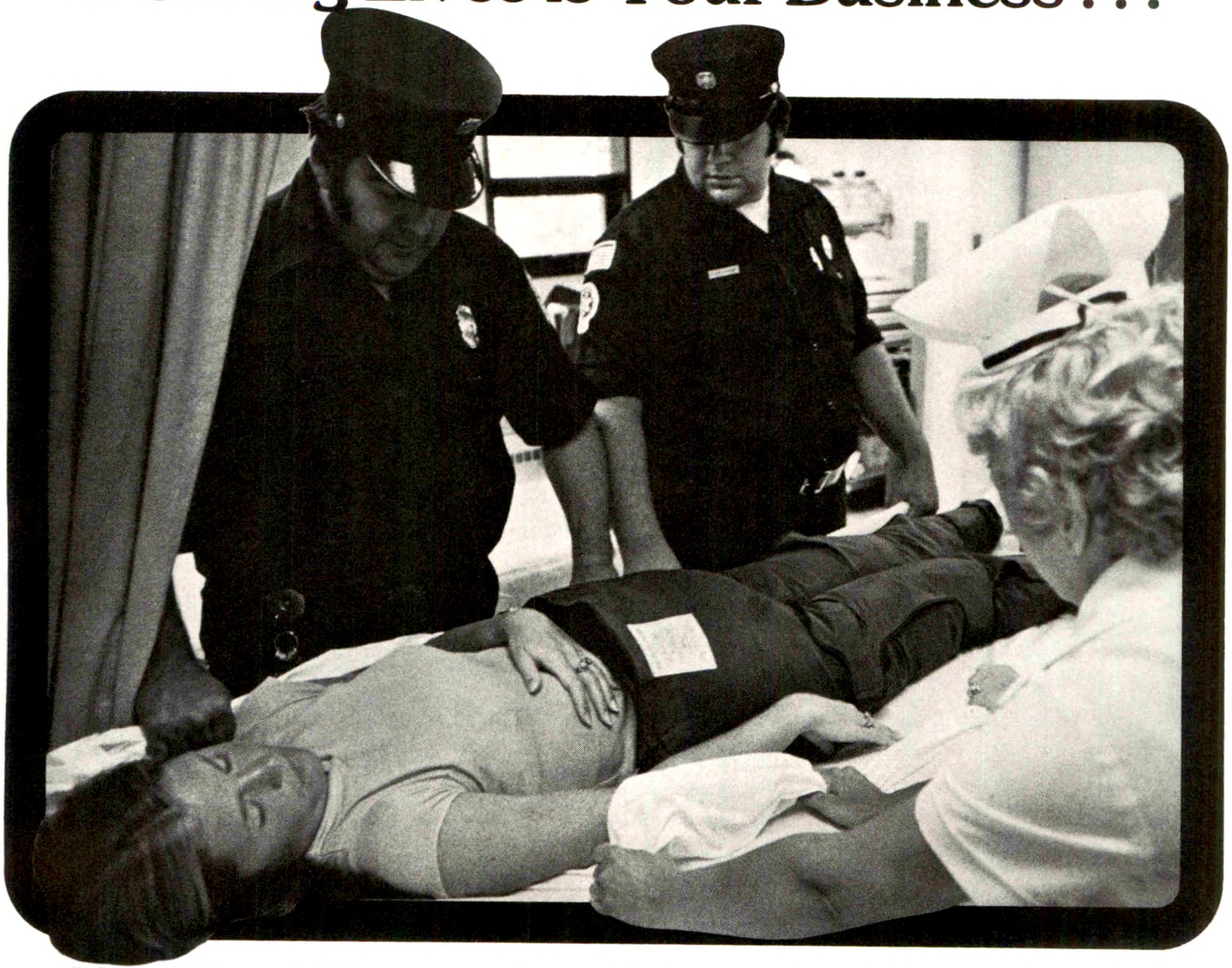
Our early interest in the management of congestive heart failure without angina has been rekindled by the recent advent of the thallium scans, and the ability to measure ejection fraction changes preoperatively in response to nitroglycerin. Using this technique, we have identified a subgroup of patients with congestive heart failure, and we have been able to demonstrate an increased ejection fraction postoperatively.

Our most common technique remains a single period of normothermic ischemic arrest. Our perioperative infarction rate remains 4%. The interval infarction rates remained steady at about 3½ to 4% *per annum*. Analysis of our data suggests to us that there are subgroups of patients who probably will benefit from some form of myocardial preservation, and we are initiating studies using isotope ejection fraction measurements to evaluate the role of the various cardioplegic solutions in these higher risk patients. But for the average patient with good ventricular function, we continue to use normothermic ischemic arrest.

In our long-term follow-up, over 80% of our patients are working. Symptomatic relief remains constant at over 90%.

We feel, therefore, that the coronary bypass is an ideal treatment for angina pectoris, and our long-term studies, clinical, angiographic, and pathologic, indicate to us that through five years at least the results are extremely durable.

If Saving Lives is Your Business . . .



You should know about life-saving MAST®

MAST is the original Medical Anti-Shock Trouser* manufactured by David Clark Company.

MAST can be positioned and applied in 60 seconds.

MAST produces rapid autotransfusion for control or reversal of shock,** and can check trauma from application right up to surgery.

MAST exclusive automatic relief valves prevent overpressurization. Eliminates necessity of constantly monitoring pressure gauges.

MAST Velcro closures provide easy operation and a snug fit for better pressure stability and patient comfort.

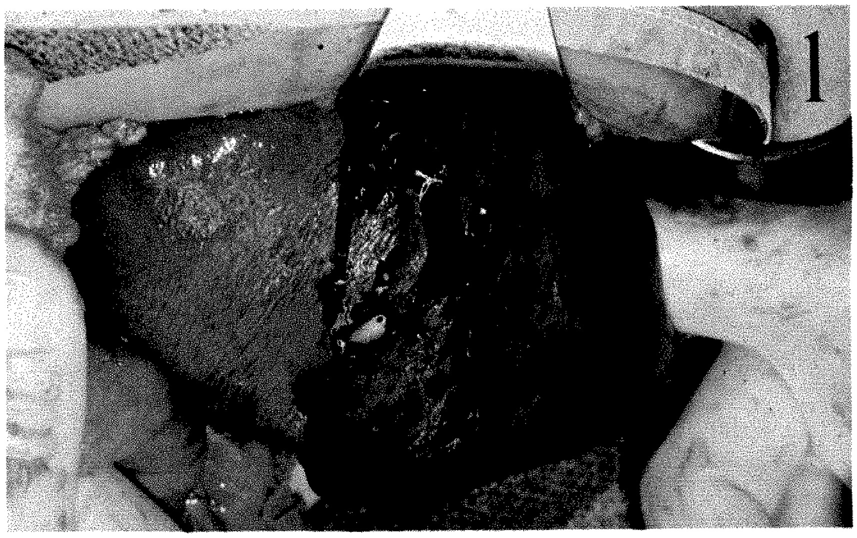
MAST can be counted on to continue to work satisfactorily in extreme heat and cold.

If you care about good Emergency Care you should know more about life-saving MAST.
Distributed nationwide. Send for FREE brochure and name of local emergency equipment suppliers.

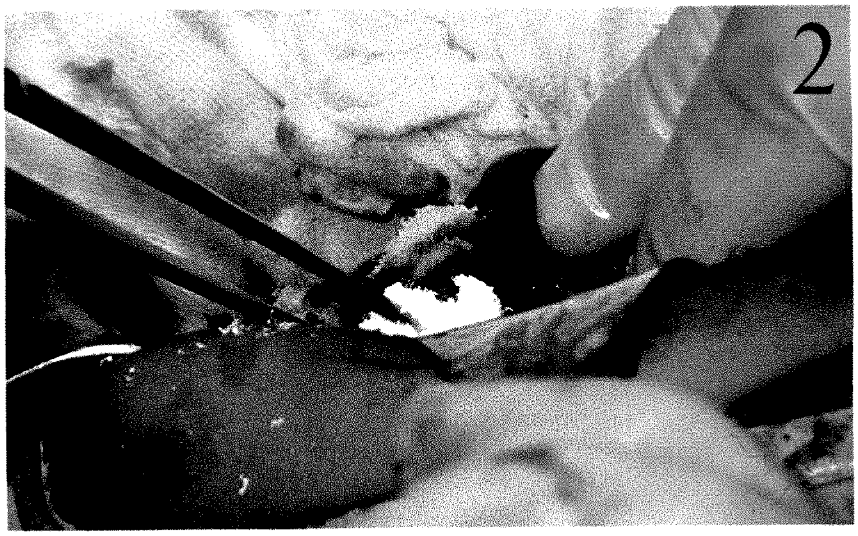
*Patent No. 3,933, 150
**Documented Case Histories available upon request.

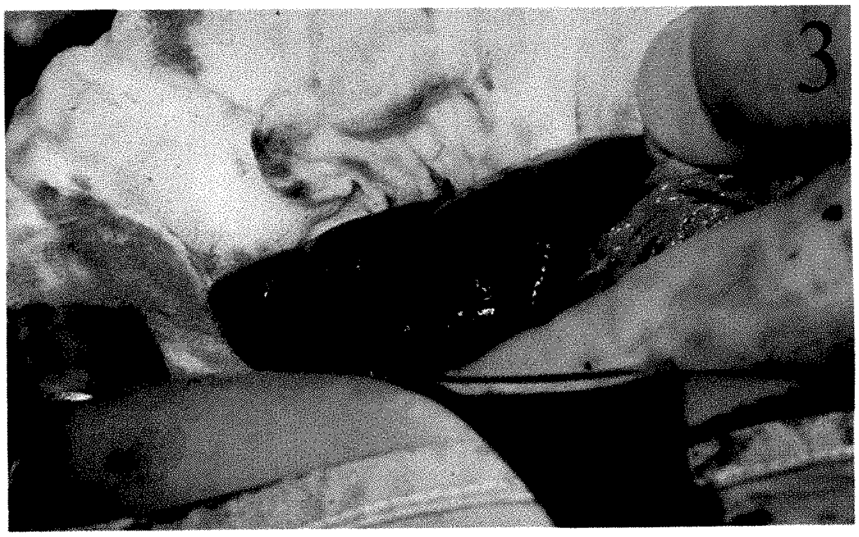
David **Clark** COMPANY
INCORPORATED
365 Franklin St., Worcester, MA 01604 (617) 756-6216

Regional Offices: Dallas, TX (214) 321-3323; Dayton, OH (513) 433-0033; Georgetown, SC (803) 546-2223;
Los Angeles, CA (213) 776-4571; Philadelphia, PA (215) 878-1905.
Distributed in Canada by Levitt Safety Ltd.



Avitene® (MCH) at work: controlling parenchymal bleeding from a lacerated spleen in a child





1. The spleen was nearly transected and a partial splenectomy was performed. Hemostatic mattress sutures were placed in the splenic capsule but there was residual bleeding from the splenic parenchyma.

2. Avitene® (microfibrillar collagen hemostat) was applied directly to the bleeding surface with dry forceps. Using a dry sponge, moderate pressure was maintained for 5 to 7 minutes.

3. With bleeding controlled, excess Avitene was teased off the surface of the spleen. The remaining portion of the spleen was not resected. Recovery from partial splenectomy was uneventful.

Please see facing page for brief summary.

Avitene®

Microfibrillar Collagen Hemostat

Avitene® (microfibrillar collagen hemostat), derived from purified bovine corium, differs physically, chemically, and clinically from other topical hemostats. Supplementing conventional hemostatic techniques, Avitene extends your range of options when surgical bleeding problems are encountered. In cases where sutures, cautery, or pressure are impractical or ineffective, Avitene...

...a modified natural collagen, triggers the normal hemostatic mechanism, and produces a normal (physiologic) clot

...adheres tenaciously, even to irregular bleeding surfaces

...controls generalized bleeding from soft, friable tissues and highly vascularized organs

...produces minimal foreign body response

...is effective in most patients receiving heparin or aspirin, and in those who are moderately thrombocytopenic.

Numerous clinical studies document the efficacy of Avitene in a wide range of surgical procedures. Reprints of these studies and films showing surgeons using Avitene (microfibrillar collagen hemostat) are available at your request. Films currently available include: **(1)** Six Demonstrations of Effectiveness; **(2)** Use in Partial Nephrectomy; **(3)** Use in Thoracic Surgery; **(4)** Use in Neurosurgery; and **(5)** Use in Bone Bleeding.

For further information, write:
Medical Director, Avicon, Inc., P.O. Box 85,
Fort Worth, Texas 76101.

Avicon Avitene® is distributed by
Alcon Laboratories, Inc.

HOW TO USE AVITENE®

Keep Avitene dry. Care must be taken to ensure that Avitene is kept scrupulously dry, as prolonged exposure to moisture will impair its hemostatic efficacy. It will adhere to any wet surface and should be applied only with dry smooth forceps.

Apply Avitene directly to the source of the bleeding. It is important that Avitene be applied directly to the source of bleeding. Otherwise Avitene may seal over the exit site of deeper hemorrhage and conceal an underlying hematoma. Surfaces to be treated should first be compressed with dry sponges, and then covered with Avitene. The amount required will depend on the force and severity of the bleeding.

Apply pressure with a dry sponge. It is then necessary to apply moderate pressure over the Avitene with a dry sponge. The period of time necessary will vary with the severity of the bleeding, and may range from a minute for capillary bleeding, to three to five minutes for brisk bleeding or arterial leaks. For control of oozing from cancellous bone, Avitene should be firmly packed into the spongy bone surface.

Remove excess Avitene. After five to ten minutes, excess Avitene should be teased away; this can usually be accomplished without initiating rebleeding. If breakthrough bleeding occurs in areas of thin application, additional Avitene may be applied. The amount required depends, again, on the severity of bleeding. In capillary bleeding, one gram will usually be sufficient for a 50 cm² area. Thicker coverage may be required for brisk bleeding.

Avitene® (microfibrillar collagen hemostat)

Description: Avitene is an absorbable topical hemostatic agent prepared as a dry, sterile, fibrous, water insoluble partial hydrochloric acid salt of purified bovine corium collagen.

Indications: Avitene is used in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

Contraindications: Avitene should not be used in the closure of skin incisions as it may interfere with the healing of the skin edges.

Warnings: Avitene is inactivated by autoclaving. Ethylene oxide reacts with bound hydrochloric acid to form ethylene chlorohydrin. This product should not be resterilized. It is not for injection. Moistening Avitene or wetting with saline or thrombin impairs its hemostatic efficacy. It should be used dry. Discard any unused portion. As with any foreign substance, use in contaminated wounds may enhance infection.

Precautions: Only that amount of Avitene necessary to produce hemostasis should be used. After several minutes, excess material should be removed; this is usually possible without the re-initiation of active bleeding. Avitene contains a low, but detectable, level of intercalated bovine serum protein which reacts immunologically as does beef serum albumin. Increases in anti-BSA titer have been observed following treatment with Avitene. About two-thirds of individuals exhibit antibody titers because of ingestion of food products of bovine origin. Intradermal skin tests have occasionally shown a weak positive reaction to BSA or Avitene but these have not been correlated with IgG titers to BSA. Tests have failed to demonstrate clinically significant elicitation of antibodies of the IgE class against BSA following Avitene therapy. Care should be exercised to avoid spillage on nonbleeding surfaces, particularly in abdominal or thoracic viscera. Teratology studies in rats and rabbits have revealed no harm to the animal fetus. There are no well-controlled studies in pregnant women; therefore, Avitene should be used in pregnant women only when clearly needed.

Adverse reactions: The most serious adverse reactions reported which may be related to the use of this drug are potentiation of infection including abscess formation, hematoma, wound dehiscence, mediastinitis. Other reported adverse reactions possibly drug related are adhesion formation, allergic reaction, foreign body reaction, subgaleal seroma (report of a single case).

How supplied: In 1 g and 5 g sterile jars of sterile microfibrillar collagen hemostat all contained in sealed can. Sterility of the jar's exterior cannot be guaranteed if can seal is broken. Content of jar is sterile until opened.

6/78

Practical guidance in challenging situations

HARRISON, GITTES, PERLMUTTER, STAMEY & WALSH: **Campbell's Textbook of Urology,**
Volume I–4th Edition

This first of a three volume master work will present today's best insight into all aspects of urologic disorders and diseases. Completely revised and up-dated, Volume I brings you vital data on anatomy and physiology, examination and diagnostic techniques, pathophysiology, infections and inflammations, infertility, injuries, tumors of the genitourinary tract in the adult, and more. No physician who deals with urologic disorders should be without it.

Edited by **J. Hartwell Harrison**, MD, Elliott Carr Cutler Prof. of Surgery Emeritus, Peter Bent Brigham Hospital; **Ruben F. Gittes**, MD, Chief of Urology, Peter Bent Brigham Hospital; Prof. of Urologic Surgery, Harvard Medical School; **Alan D. Perlmutter**, MD, Chief of Pediatric Urology; Children's Hospital of Michigan; Prof. of Urology, Wayne State Univ. School of Medicine; **Thomas A. Stamey**, MD, Prof. of Surgery and Chairman of Urology, Stanford Univ. School of Medicine; and **Patrick C. Walsh**, MD, Urologist-in-Chief, The Johns Hopkins Hospital; Prof. and Director of Urology, The Johns Hopkins University School of Medicine. About 975 pp., 570 ill. About 50.00. Ready July 1978. **Order #4540-2.**

BROMAGE: **Epidural Analgesia**

Examining both the clinical and the laboratory understanding of this essential technique, which involves less risk of neurologic complications than does spinal anesthesia, the author teaches how best to use the epidural blockade. Special emphasis is on its use in obstetrical practice and in the management of chronic pain. Coverage ranges from anatomy, pharmacology, and physiology, to surgical and therapeutic applications, and complications.

By **Philip R. Bromage**, MB, FFARCS, FRCP(C), Prof. of Anesthesiology and Prof. of Obstetrics and Gynecology, Duke Univ. Medical Center. About 720 pp., 275 ill. About $30.00 Ready July 1978. **Order #2005-1.**

REECE: **Reece—Chamberlain Manual of Emergency Pediatrics,** *2nd Edition*

Totally reorganized in a 2nd edition, this manual now features many additional contributors. Its format has been renovated too—divided into individual sections examining True Emergencies—Diagnosis and Treatment, Presenting Complaints (Signs and Symptoms of Disease), Diagnostic Entities, and Procedures and Therapeutics. All discussions are thoroughly up-to-date.

Edited by **Robert M. Reece**, MD, Assoc. Prof. of Pediatrics, Boston Univ. School of Medicine; Chief, Pediatric Walk-In Clinic, Boston City Hospital; with about 30 contributors. About 500 pp. Illustd. Soft cover. Ready July 1978. **Order #7498-4.**

To order titles on 30-day approval, enter order number and author:

6/78 AOS

☐	☐	☐
AU:	**AU:**	**AU:**

FULL NAME

POSITION & AFFILIATION (IF APPLICABLE)

ADDRESS

CITY **STATE** **ZIP**

☐ check enclosed ☐ bill me

Prices U.S.A. only and subject to change.

W.B.Saunders Co.
West Washington Square, Philadelphia, PA 19105

BATEMAN: **The Shoulder and Neck,**
2nd Edition

Completely updated, this new 2nd edition remains the definitive guide to the systematic diagnosis and practical therapy of all disorders of the closely interrelated head and neck regions. The assessment of disability is treated in depth. Surgical techniques are clearly illustrated. Rehabilitative measures are detailed. All aspects of these problems are examined.

By **James E. Bateman**, MD, FRCS(C), Diplomate American Board of Orthopedic Surgery; Surgeon-in-Chief, Orthopedic and Arthritic Hospital, Toronto. About 850 pp., 810 ill. About $45.00. Ready July 1978. **Order #1571-6.**

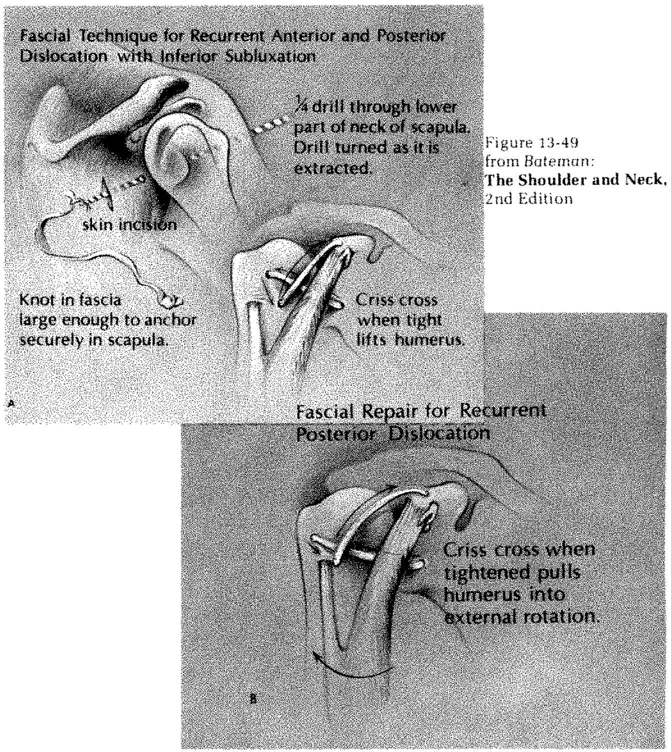

Fascial Technique for Recurrent Anterior and Posterior Dislocation with Inferior Subluxation
¼ drill through lower part of neck of scapula. Drill turned as it is extracted.
skin incision
Knot in fascia large enough to anchor securely in scapula.
Criss cross when tight lifts humerus.
A
Fascial Repair for Recurrent Posterior Dislocation
Criss cross when tightened pulls humerus into external rotation.
B

Figure 13-49
from *Bateman:*
The Shoulder and Neck,
2nd Edition

SCHWARTZ et al.: **Principles and Practice of Emergency Medicine**

The specialty of emergency medicine finally has a comprehensive and definitive text that explores its many facets. Over 1600 pages of expert medical discussion focus on topics from the pathophysiologic basis of acute illness and injury to special problems in trauma, such as burns, lasers, radiation, etc. Emergency medical procedures, non-traumatic medical emergencies, emergency medical support systems, legal and socio-economic factors are covered too.

Edited by **George R. Schwartz**, MD, Univ. of New Mexico School of Medicine; with associate editors: **Peter Safar**, MD, Univ. of New Mexico School of Medicine; **John H. Stone**, MD, Univ. of Pittsburgh School of Medicine; **Patrick B. Storey**, MD, Univ. of Pennsylvania School of Medicine; and **David K. Wagner**, MD, Medical College of Pennsylvania; with about 130 contributors. About 1,650 pp., 365 ill. Ready July 1978. Single volume: About $70.000. **Order #8031-3.**
Two-volume set: About $80.00 **Order #8034-8.**

RICH & SPENCER: **Vascular Trauma**

This book gives detailed descriptions of a number of vascular injuries, including a thorough review of their history, incidence and nature. Authoritatively presented, it contains a wealth of historical, statistical, and clinical information describing the etiology, pathology, diagnostic methods, management, results, and follow-up of a variety of arterial and venous injuries. Major vessels are emphasized.

By **Norman M. Rich**, MD, Col., MC, USA, Chief, Peripheral Vascular Surgery Service, Walter Reed Army Medical Center; Prof. and Chairman of Surgery, Uniformed Services Univ. of the Health Sciences; and **Frank C. Spencer**, MD, George David Stewart Prof. of Surgery and Chairman of Surgery Dept., New York Univ. School of Medicine. About 610 pp., 500 ill. $38.50. April 1978. **Order #7580-8.**

Some surgeons used to throw away our single-use instruments...before they used them.

We've come a long way since the early days when single-use special procedures instruments were more like toys than something you'd take seriously.

There's an important difference with Acme United GENERATION II instruments: they work.

Our GENERATION II scissors cut, even at the tip. Our GENERATION II hemostats hold, without overbiting. Our GENERATION II needle holders grip, without slippage.

On your rounds or in the ER, you might find our single-use sterile-packed trays and instruments the best things you can put your hands on.

You'll find an impressive range of Acme United GENERATION II instruments: scissors, hemostats, needle holders, towel clamps and forceps, packaged in 22 different configurations. With a line this versatile, we can even make up special dressing trays to suit your particular needs and specifications.

GENERATION II single-use instruments by Acme United are a serious step forward in the battle to cut costs, and lower cross contamination risks, liability and pilferage.

That they save money for your hospital is important. That they work well for you is imperative.

Acme United GENERATION II
Single-use instruments that get used.

Acme United Corporation
Medical Products Division
Bridgeport, Connecticut 06609

A new generation of instruments awaits your challenge.

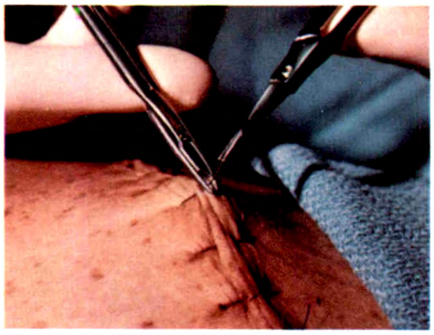
You are quite right in being skeptical about single-use special procedures instruments. Patient and procedure must come ahead of everything—cost, liability, even cross-contamination risk. And, frankly, all too often, the quality of single-use instruments offered little to advance their cause.

New: GENERATION II from Acme United. Now, there's a new generation of special procedures instruments from Acme United: GENERATION II. They perform. They work. They come through. For what they do—a one-time performance—they compare quite favorably with reusable instruments costing up to a hundred times more. All we've left out is the durability, the expensive finishing, the extra toughness to withstand repeated use and extended battles in the sterilizer.

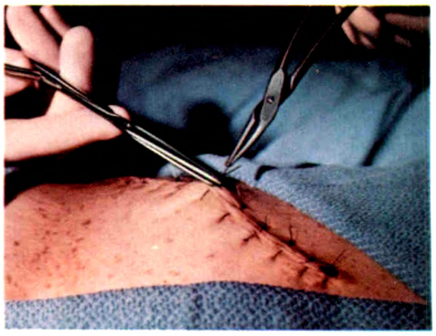
Please fill out the attached card and let us send you any of our special procedures instruments for your evaluation. Put them to any kind of test you choose. If you're not impressed, throw them away once and for all. If you're pleased with them, as we believe you will be, please ask for more.

Acme United
GENERATION II
Single-use instruments
that get used.

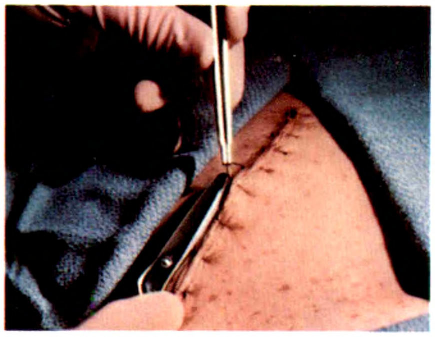
The GENERATION II challenge: item by item, they work.



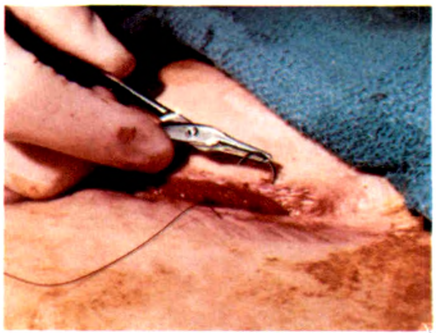
GENERATION II Scissors cut. Custom forged and precision-ground of nickel-plated steel to give you a keen cutting edge. Available in a wide variety, including an exclusive 4½" fine point tissue scissor, Littauer, and sharp/sharp and sharp/blunts in 4½" and 5½" sizes.



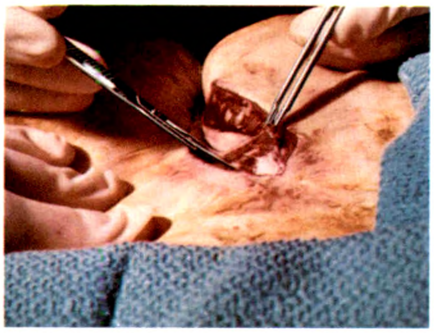
GENERATION II Hemostats clamp tight. Light but strong, Acme United hemostats are engineered precisely to meet and lock in a tight, sure, non-overlapping grip. In two sizes of straight, and two of curved.



GENERATION II Forceps hold. All metal, carefully aligned to give you a firm, sure, precise grip.



GENERATION II Needle holders clutch. Precise jaw alignment lets you pull needle and suture through the skin without locking first. Even the smallest of needles and the finest of sutures can be gripped and pulled.



GENERATION II Scalpels feel right. Nickel-plated steel handles deliver the heft of reusable scalpels. Razor-sharp blades are pre-assembled and plastic-shielded for safety and convenience.

GENERATION II Trays protect. Protect against cross-contamination, against pilferage, against damage, against liability, against spiraling costs.

Photographed at the University of Kentucky Medical Center, Lexington, Kentucky.

©1978 Acme United Corporation

Factors Influencing Late Survival After Coronary Bypass Surgery

GERALD M. LAWRIE, M.D., GEORGE C. MORRIS, JR., M.D.

From the Department of Surgery, Baylor College of Medicine, Houston, Texas

In order to determine which factors most influence late survival after the coronary bypass procedure, a review was made of the initial experience of one surgeon who performed 792 operations between 1968 and 1972. The initial 250 patients were compared with the subsequent 542 patients. The two groups were of similar age and sex and had a similar distribution of coronary disease and impaired left ventricular function. Perioperative mortality fell from an initial 6.8% (17/250) to 4.8% (26/542). The number of grafts per patient was initially 1.5 but later was 1.8. Graft patency beyond five years in 105 patients was 88.6% (148/167), 96.2% of patients had at least one patent graft. Initially, crude five year survival was 78.0% (195/250) but was 87.8% (476/542) in the later group. Patients who had no residual unbypassed lesions after operation had a 91.4% (287/314) survival while those with two residual lesions had a 66.7% (14/21) survival. Those patients with a preoperative end-diastolic pressure of less than 15 mmHg and no localized abnormality of contraction had a five year crude survival of 92.1% (316/343) whereas the patients with poor ventricular function had a survival of 81.8% (108/132). Our conclusion is that the most important factors determining late survival are the quality of surgical result achieved as shown by: perioperative mortality and graft patency; the degree of revascularization established; and the preoperative status of left ventricular function. The number of vessels diseased preoperatively had a minimal influence on late survival. These findings emphasize the primary importance of good surgical results in obtaining superior late survival rates.

THE VALUE OF THE CORONARY bypass procedure in the relief of angina pectoris unresponsive to medical therapy is now widely accepted.[7,12,17] The influence of coronary bypass on survival, however, has remained uncertain except for disease of the left main coronary artery where a superior survival in surgically treated patients with this condition is now well recognized.[24]

The conclusion of the recently published V. A. Cooperative study[18] that surgery has not prolonged survival in a highly selected group of patients with chronic stable angina has created much controversy, mainly because of the poor surgical results with which the medical results were compared. It has been suggested, however, that the surgical results reported were of an acceptable quality for the period 1972–1974 and that the subsequent improvement in results for operation which have been reported more recently are attributable to selection of better risk patients and not due to increasingly skillful surgical management of patients with equally extensive disease.[2,18]

Because in our own experience the late results of coronary bypass have been far more favorable than those reported in the V.A. Cooperative study, we were interested to examine in detail the fate of a large group of patients operated upon before the V.A. Cooperative study surgical series was begun and to determine the factors which appear to have influenced survival of these patients at a follow-up beyond five years. In particular, by comparing the results in our initial experience with those achieved subsequently we have been able to examine the influence of increasing surgical experience on late survival.

Material and Methods

Between 1968 and 1972, one surgeon (GCM) performed a consecutive series of 792 aortocoronary bypass procedures using saphenous vein. The only patients excluded from this consecutive series were those who had received valve prostheses (21 patients). The techniques employed have been reported previously.[15,16]

There were 703 men and 89 women. The mean age at operation was 50.1 years (range 26–75 years). The indication for operation was angina pectoris with associated discrete coronary lesions of >70% stenosis in 96.0% (760/792) of patients. In 4.0% (32/792), congestive heart failure alone was present. In 20.7% (164/792) of patients, both angina and congestive heart failure were present. Unstable angina pectoris was present in 14.3% (113/792) of patients. A history of previous myocardial infarction was obtained from

---

Presented at the Annual Meeting of the Southern Surgical Association, December 5–7 1977, Hot Springs, Virginia.

0003-4932-78-0600-0665-0115 © J. B. Lippincott Company

TABLE 1. *Distribution of Disease*

Vessels Involved	1968–71	1971–72	1968–72
1	23.3% (58/250)	19.0% (103/542)	20.3% (161/792)
2	44.4% (111/250)	41.9% (227/542)	42.7% (338/792)
3	26.5% (66/250)	30.8% (167/542)	29.4% (233/792)
LM	6.0% (15/250)	8.3% (45/542)	7.6% (60/792)

59.0% (467/792) of patients. Single vessel disease (>70% stenosis) was present in 20.3% (161/792), double vessel in 42.7% (338/792), triple vessel in 29.4% (233/792) and left main stenosis >50% in 7.5% (60/792) of patients (Table 1).

Preoperative ventricular function was classified as either good or poor. Poor left ventricular function was defined as an end-diastolic pressure of >15 mmHg and/or a discrete area of akinetic or aneurysmal left ventricular wall. Good left ventricular function was defined as an end-diastolic pressure of <15 mmHg and no localized motion change, regardless of other changes. Other more subjective and less reproducible criteria such as visual estimation of increased left ventricular size, hypokinetic areas, and decreased ejection fraction were not utilized, although it should be noted that ventricular function was abnormal in 71.2% (564/792) of patients if all the more subjective criteria were employed. Further, no patients, regardless of the extent of impaired left ventricular function, were excluded from this series. Indeed, at that time we were particularly interested in the influence of coronary bypass on advanced left ventricular failure.[14] Thus, patients with diffuse severe impairment of contractility and end-diastolic pressures of up to 50 mmHg are included in this series as are 23 patients who underwent concomitant left ventricular aneurysmectomy. By the criteria defined, however, good left ventricular function was present in 67.5% (535/792) of patients and poor function in 32.5% (257/792).

The patients were divided into two groups. An initial 250 patients who underwent operation between 1968 and 1971 and who represent the initial experience with this procedure during which a standardized surgical technique was evolved; and a subsequent 542 patients operated on between 1971 and 1972. The two groups were similar as to the age and sex of the patients, and in the distribution of coronary disease (Table 1) and the overall incidence of ventricular impairment (Table 2), although the severity of ventricular impairment was greater in the later group (Table 2).

TABLE 2. *Incidence of Poor Ventricular Function*

Vessels Involved	1968–71	1971–72	1968–72
1	12.1% (7/58)	20.4% (21/103)	17.4% (28/161)
2	44.1% (49/111)	29.1% (66/227)	34.0% (115/338)
3	36.3% (24/66)	40.7% (68/167)	44.6% (92/233)
LM	33.3% (5/15)	37.8% (17/45)	36.7% (22/60)
Total	34.0% (85/250)	31.7% (172/542)	32.5% (257/792)

An EDP of >25 mmHg was present in 10.5% (9/85) of patients operated upon between 1968–1971 and in 25.0% (43/172) of patients between 1971–1972.

TABLE 3. *Late Graft Patency*

	1968–71	1971–72	1968–72
Interval (range) (months)	69.5 (60–88)	66.9 (60–78)	67.7 (60–88)
No. patients	78	27	105
Graft patency	90.5% (105/116)	84.3% (43/51)	88.6% (148/167)
At least one graft patent	97.4% (76/78)	92.6% (25/27)	96.2% (101/105)
All grafts patent	85.9% (67/78)	74.1% (20/27)	82.9% (87/105)

Of the 792 patients, 121 had died 0–60 months (mean 30.7 months) postoperatively. Of the 671 survivors 98.2% (659/671) were contacted, all more than 60 months after operation.

In 105 patients, angiographic studies of graft patency were performed at a mean interval of 67.7 months (60–88 months) postoperatively (Table 3). Overall, 31.7% (251/792) of patients had undergone restudy at some time postoperatively. For comparison, the graft patency in 488 patients from the total experience with this procedure is shown in Table 4. The number of grafts performed per patient was determined for each disease pattern (Table 5). The patients then were classified according to the number of significant residual coronary lesions present, a residual lesion being defined as a lesion >70% without a patent bypass graft attached distal to it (Table 6). In classifying the 251 patients who were restudied, the presence of occluded grafts was incorporated in the results.

The survival rates of the patients were then classified according to the number of residual lesions present and the status of left ventricular function (Table 7).

The five year survival rate was determined for a group of normal subjects of an age and sex distribution identical to the 792 patients in this report.[3] The survival of this normal sample was 92.7% at five years.

Results

Perioperative Mortality

The perioperative mortality for the entire group was 5.4% (43/792) between 1968 and 1972. As can be seen from Table 8 the perioperative mortality was reduced

TABLE 4. *Graft Patency Total Experience*

	Interval	No. Pts	L	R	C	Total
	0–6	110	86.4% (76/88)	82.4% (56/68)	79.3% (23/29)	83.8% (155/185)
	7–12	38	69.7% (23/33)	82.6% (19/23)	75.0% (6/8)	76.6% (49/64)
	13–24	101	79.6% (74/93)	83.9% (52/62)	77.8% (28/36)	80.6% (154/191)
	25–36	62	85.7% (48/56)	72.7% (32/44)	80.9% (17/21)	80.1% (97/121)
	37–48	37	93.8% (30/32)	87.0% (20/23)	90.9% (10/11)	90.9% (60/66)
	49–60	43	88.6% (31/35)	80.0% (20/25)	66.7% (4/6)	83.3% (55/66)
	61–80	97	85.3% (58/68)	92.9% (39/42)	88.2% (15/17)	88.2% (112/127)
Total		488	83.9% (340/405)	82.9% (238/287)	80.5% (103/128)	83.2% (682/820)
				Asymptomatic Patients		
Total	1–88	144	94.4% (118/125)	88.6% (78/88)	93.2% (55/59)	92.3% (251/272)

Overall, 93.4% (456/488) had one or more patent grafts and 76.4% (373/488) had all grafts patent.

by 29.4% in the later group despite a greater severity of left ventricular abnormality in this group (Table 9). This is attributed mainly to fewer technical problems in the later experience. A change from femoral perfusion to cannulation of the ascending aorta eliminated the problem of aortic dissection which had occurred in two patients. It quickly became apparent that elective operation should be avoided in the presence of recent acute myocardial infarction. Excluding those patients with left main stenosis and those who underwent left ventricular aneurysmectomy, the overall perioperative mortality was 4.4% (31/708) and was reduced from an initial 5.5% (13/234) to 3.8% (18/474) between 1971 and 1972 (Table 10).

Late Survival

The overall five year survival increased from 78.0% (1968–1971) to 87.8% (1971–1972), (Table 8, Fig. 1). This improved survival was due not only to the reduction in perioperative mortality but also to a marked reduction (by 44.5%) in late attribution (Table 8, Fig. 1). Excluding patients with left main stenosis and left ventricular aneurysmectomy, the surgical rates for the remaining patients are shown in Table 11, and Figures 2 and 3. The results are tabulated for each pattern of coronary disease and according to the state of left ventricular function.

Postoperative survival rates were similar for patients with single, double and triple vessel disease with poor left ventricular function. In patients with good left ventricular function, survival rates were again similar for single and double vessel disease. The survival in the triple vessel group was depressed by an excessively high incidence of noncardiac deaths: two from cancer, three fatal strokes, and one accidental death. These six deaths accounted for 60% (6/10) of the known noncardiac deaths in only 21.3% (101/475) of the patients. Thus, if these deaths are excluded, survival in the triple vessel group was 91.1%. These results suggest that following operation late survival is determined more by preoperative left ventricular function than by the preoperative extent of coronary disease (Fig. 4). Although there was a stepwise increase in preoperative mortality from 0% in one vessel disease to 6.8% in three vessel disease, the subsequent attrition rates are quite similar for patients in each category of ventricular function (Fig. 3).

It is also of interest that the overall *five* year survival rates in these patients compare favorably with the published *two* year survival rates for the medically treated patients in the V.A. Cooperative study (Table 11).[6]

Completeness of Revascularization and Graft Patency

The number of grafts performed for each pattern of coronary disease is indicated in Table 5. It is apparent that in the 1971–1972 group more grafts were performed per patient for double and triple vessel disease and left main disease. This increased number of grafts per patient produced more complete revascularization in the later group of patients (Table 6). Between 1968–71, 75.3% (177/235) of patients had double and triple vessel disease and postoperatively only 15.0% had two residual lesions. Between 1971–1972, 79.3% (394/497) had double and triple vessel disease but the postoperative incidence of double and triple vessel residual

TABLE 5. *Completeness of Revascularization*

	No. of Grafts/Patient	
No. Vessels Diseased	1968–71	1971–72
1	1.0	1.0
2	1.6	1.8
3	1.8	2.2
LM	1.7	2.0
Overall	1.5	1.8

TABLE 6. *Influence of Revascularization on the Number of Unbypassed Lesions*

Vessels Involved	1968–71 Pre-op	1968–71 Post-op	1971–72 Pre-op	1971–72 Post-op
0	—	55.2% (129/235)	—	66.2% (329/497)
1	24.7% (58/235)	30.0% (71/235)	20.7% (103/497)	29.0% (144/497)
2	47.2% (111/235)	15.0% (35/235)	45.7% (227/497)	4.4% (22/497)
3	28.1% (66/235)	—	33.6% (167/497)	0.4% (2/497)

Postoperative figures include results of graft patency in 251 patients.

lesions was reduced to 4.4% from the 15.0% between 1968–1971 (Table 6). This is despite a somewhat lower graft patency in the later group (84.3% vs. 90.5%) Table 3).

From the total experience with this procedure, graft patency determinations had been made at some time postoperatively in 488 patients with 820 grafts. The overall patency rate was 83.2% (682/820) compared with the patency rate of 92.3% (251/272) in completely asymptomatic patients. Overall 93.4% of patients had one or more patent grafts while 76.4% had all grafts patent (Table 4).

The results in Table 7 indicate again that for a given level of ventricular function, the later survival depended primarily on the extent of postoperative residual disease rather than the initial number of vessels diseased. That is comparable survival rates were obtained for patients with no residual lesions, while survival was significantly impaired when residual lesions remained after operation. It is also of interest that only one patient was identified with three residual lesions.

Discussion

Over the last 13 years, the coronary bypass procedure has achieved increasingly widespread recognition as a highly effective form of therapy for the relief of angina pectoris. Many clinical reports have confirmed this both for stable and unstable angina with about 90% of patients reporting improvement or complete relief more than five years after operation.[1,2,7–12,15–17,21,23]

The influence of the coronary bypass on late survival has been less clear. In patients with left main stenosis it is now generally accepted that surgical treatment provides superior late survival rates and this has been confirmed by a randomized prospective study.[24] In patients with single, double and triple vessel disease, the influence of operation on survival has been less well established.

In the experience presented in this study, the late survival rates beyond five years in the group of patients operated upon between 1971 and 1972 are markedly similar to the early two year survival rates reported for the medically treated group of patients of the V.A. Cooperative study.[6] The patients in our study with good left ventricular function had essentially normal survival rates beyond five years (Table 11, Fig. 3). As the medical results of the V.A. study are the best ever reported for a medically treated series, and as all their patients were suitable for operation we consider that the markedly superior late survival rates we obtained after operation to be highly significant.

It is apparent from Tables 1 and 2 that the two groups of patients presented in this study were clinically very similar. It is of great interest therefore that the later group of patients (1971–1972) have had markedly superior postoperative survival rates. Examination of our data suggests to us that following the coronary bypass operation, late survival is determined to a very large extent by three factors: the skill and experience of the surgeon which is reflected in the operative mortality, perioperative infarction rate and graft patency rate; the completeness of revascularization of the three major vessel systems which has been achieved; and the preoperative status of left ventricular function. Of these three variables, only the last, at present, is completely beyond the control of

TABLE 7. *Influence of Postoperative Residual Disease on Five Year Survival (1971–1972)**

	No. of Residual Lesion (474 Pts)†		
Left ventricular function	0–66.2% (314/474)	1–29.1% (138/474)	2–4.4% (21/474)
Good	93.5% (202/216)	88.6% (62/70)	72.2% (13/18)
Poor	86.7% (85/98)	64.8% (57/88)	33.3% (1/3)
Overall	91.4% (287/314)	75.3% (119/158)	66.7% (14/21)

* Left main disease and left ventricular aneurysm resection excluded.

† 1 patient had three residual lesions.

TABLE 8. *Overall Mortality*

	1968–71	1971–72	1968–72
Perioperative (30d)	6.8% (17/250)	4.8% (26/542)	5.4% (43/792)
Late	15.2% (38/250)	7.4% (40/542)	9.8% (78/792)
Overall	22.0% (55/250)	12.2% (66/542)	15.3% (121/792)
Overall survival	78.0% (195/250)	87.8% (476/542)	84.7% (671/792)

From 1971–72 perioperative mortality was reduced by 29.4% and the late mortality reduced by 44.5%.

the surgeon in any individual patient and improvement here raises important general questions as to how best to prevent significant impairment of left ventricular function in coronary artery disease.

The deleterious influence on late survival of preoperative impairment of left ventricular function is emphasized by Tables 7 and 11 and Figures 3 and 4. These findings suggest to us the importance of avoiding progressive loss of myocardial tissue by either chronic severe ischemia or recurrent acute myocardial infarction. The knowledge that an essentially normal survival rate can be achieved after operation in the presence of normal ventricular function places a heavy responsibility upon us to avoid, where possible, the progressive deterioration of a patient on medical therapy into an unfavorable and irreversible state of left ventricular impairment.

In contrast to our favorable late survival with operation, the preliminary survival results of the V.A. Cooperative study[18] have been interpreted as showing that medical and surgical therapy for chronic stable angina will achieve comparable late survival rates.

This study suffers from deficiencies which make its conclusions subject to serious question. The patients represent a highly selected group. The presence of any of the following conditions led to exclusion from the study: myocardial infarction less than six months before operation; persistent diastolic hypertension despite treatment; marked cardiac enlargement; presence of left ventricular aneurysm or other significant cardiac disease such as valvular heart disease; presence of any other major disease making major surgery inadvisable or limiting life expectancy to less than five years; previous operation for angina pectoris; unstable angina or angina of increasing severity suggesting "impeding infarction;" or the presence of congestive heart failure unless clinically compensated for at least three weeks.[6]

TABLE 9. *Perioperative Mortality*

	1968–71	1971–72
MI	41.2% (7/17)	76.9% (20/26)
Evolving MI	11.8% (2/17)	—
Technical	17.6% (3/17)	—
Stroke	5.9% (1/17)	15.4% (4/26)
Arrhythmia	17.6% (3/17)	—
Respiratory	—	3.8% (1/26)
Pulmonary embolus	5.8% (1/17)	—
Ruptured aneurysm	—	3.8% (1/26)
Overall	6.8% (17/250)	4.8% (26/542)

TABLE 10. *Mortality (Excluding Left Main Disease and Left Ventricular Aneurysm Resection)*

	1968–1971	1971–1972	1968–1972
Perioperative	5.6% (13/234)	3.8% (18/474)	4.4% (31/708)
Late	15.4% (36/234)	6.1% (29/474)	7.2% (51/708)
Overall	20.9% (49/234)	9.9% (47/474)	11.6% (82/708)
Overall survival	79.1% (185/234)	90.1% (427/474)	88.4% (626/708)

These exclusions leave a group of patients whose operative risk should have been extremely low. Despite suggestions to the contrary,[2,18] an operative mortality of 5.6% was excessive in such a group of patients even between 1972 and 1974. In our own experience between 1971 and 1972 with a group of patients in which none of these exclusionary criteria were employed and in which patients with severe impairment of left ventricular function, congestive heart failure and unstable angina were all included, the operative mortality was 3.8% (Table 10) and the major proportion of the mortality was in patients with severely abnormal ventricular function (Table 9), most of whom would have been excluded from the V.A. study. This is even more apparent when one

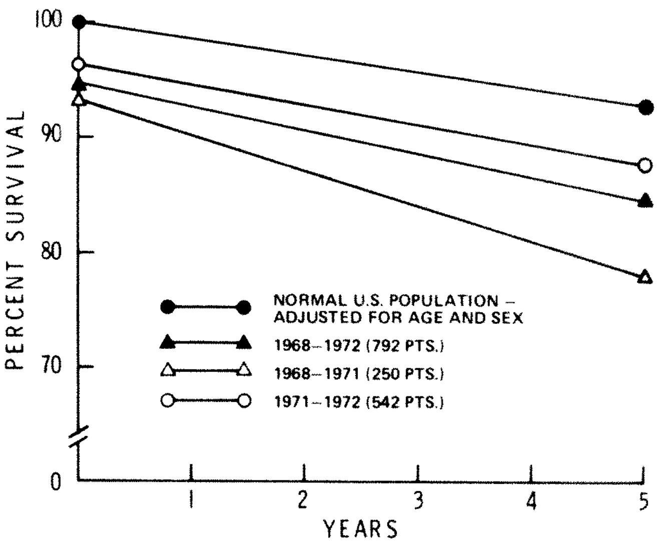


FIG. 1. Survival of all patients in this study with a matched normal population for comparison. The different survival rates between 1968–1971 and 1971–1972 are shown.

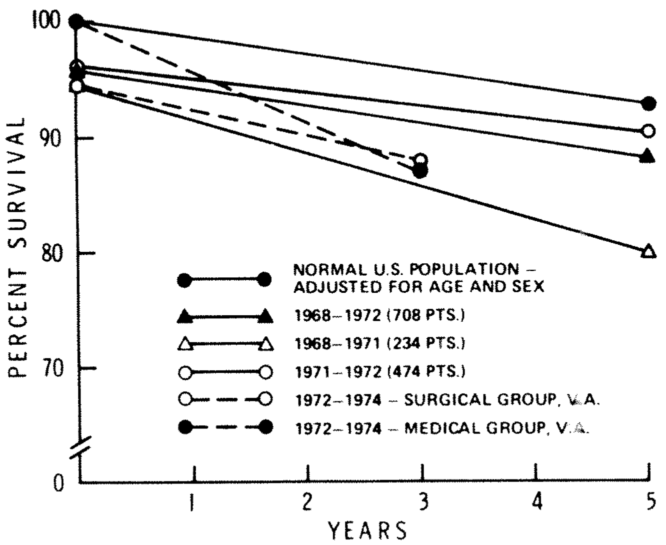


FIG. 2. Overall survival with exclusion of patients with left main disease and left ventricular aneurysmectomy. The medical and surgical survival of the V.A. Cooperative study are shown for comparison.

considers that in our initial experience between 1968 and 1971, which represented one of the earliest reported surgical series,[16] the operative mortality was only 5.5% compared with 16% for the initial V.A. period between 1970 and 1972.[20] Others have also reported operative mortalities of 3–6% for that same period in unselected series which included poorer risk patients.[1,23] The report by Conley and associates[5] on the influence of patient selection on mortality rates also suggests that for such a good-risk group that an operative mortality of 5.6% was excessive.

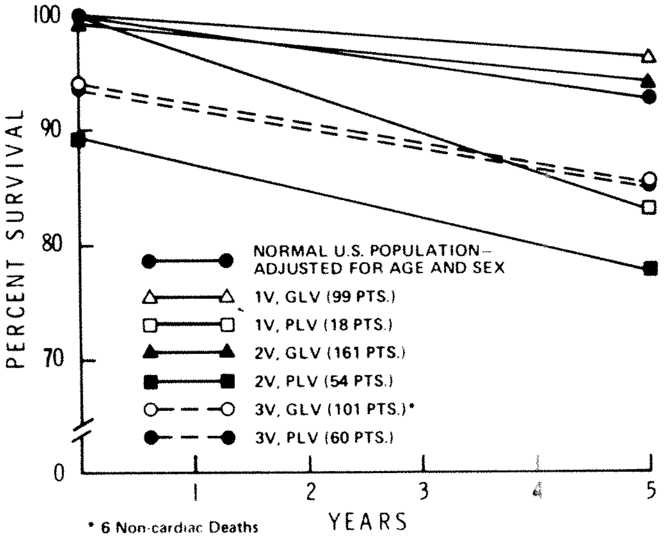


FIG. 3. Survival according to the number of significantly diseased vessels preoperatively and to preoperative left ventricular function (see text) (GLV-good left ventricle, PLV-poor left ventricle). (Left main disease and left ventricular aneurysmectomy excluded.

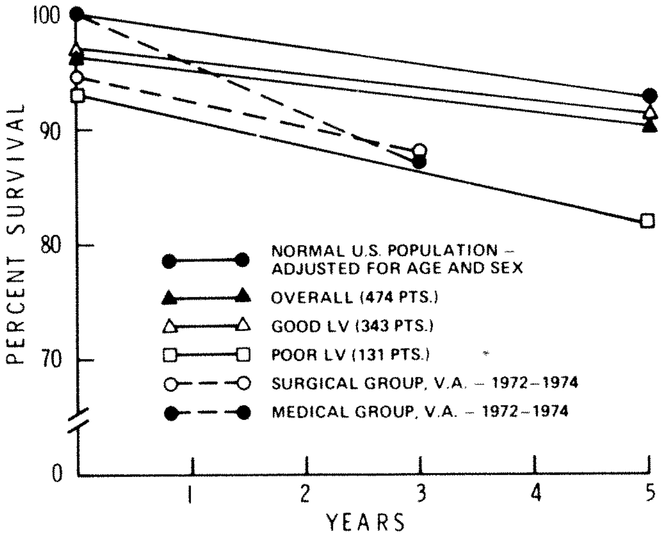


FIG. 4. Survival according to preoperative left ventricular function. (Left main disease and left ventricular aneurysmectomy excluded).

These poor results are also reflected in an inadequate overall graft patency rate of only 69%.[18] This is considerably below the patency rates of 80–90% reported from experienced centers for patients operated upon before the Veterans Administration study began.[8,15,22,23] Despite a number of grafts per patient comparable to our later experience, (Table 12), this low graft patency rate has resulted in complete surgical failure in 12% of the V.A. patients compared with 3.8–7.4% in our experience. Perhaps more significantly, only 54% of V.A. patients had all grafts patent, compared with 74.1–85.9% of our patients (Tables 3, 4, 12).

In our earlier reports on these patient concerning graft patency,[9] and pathological changes in the vein bypass grafts,[10,11] the favorable behavior of the vein grafts up to eight years after operation has been well documented. It is clear also that disease in the native coronary circulation was not accelerated by the bypass grafts.[7] The overall patency rate of 83.2% (Table 6) is lower than the 88.6% patency noted in the late studies (Table 3) and the 92.3% (Table 4) noted in a group of completely asymptomatic patients (Table 4). This emphasizes the previously reported influence of patient selection on graft patency rates.[9] Whereas in the overall group, 66.8% (548/820) of patients were symptomatic, in the patients studied beyond five years less than 50% had any residual symptoms. Thus, because the later patient group is more representative of the overall clinical experience, we believe that the true graft patency is nearer to 88.6%.

It is obvious that patients who have no patent grafts represent individuals who have been exposed to a significant operative risk without resultant benefit. How-

TABLE 11. *Five Year Survival Rates (1971–1972) (Excluding Left Main Disease and Left Ventricular Aneurysm Resection)*

No. Vessels Diseased	No. Pts	Perioperative Mortality (30d)	Overall 5 Year Survival	V.A.-Medical 2 Year Survival
1				
Good LV	81	0	96.3% (78/81)	97%
Poor LV	18	0	83.3% (15/18)	93%
Overall	99	0	93.9% (93/99)	94%
2				
Good LV	161	1.9% (3/161)	94.4% (152/161)	94%
Poor LV	54	9.3% (5/54)	77.8% (42/54)	87%
Overall	215	3.7% (8/215)	90.2% (194/215)	90%
3				
Good LV	101	5.9% (6/101)	85.2% (86/101)*	90%
Poor LV	60	8.3% (5/60)	85.0% (51/60)	86%
Overall	161	6.8% (11/161)	85.1% (137/161)	88%
Total				
Good LV	343	2.6% (9/343)	92.1% (316/343)	94%
Poor LV	132	7.6% (10/132)	81.8% (108/132)	88%
Overall	475	4.0% (19/475)	89.3% (424/475)	90%

* Two deaths from cancer, three fatal strokes, one fatal accident.

ever, the low incidence of patients with all grafts patent also is of concern. We believe that the mechanism whereby the coronary bypass operation enhances late survival is that patients are converted from high to low risk categories of coronary disease by elimination of the functional significance of a high grade stenosis by a patent graft which in effect reduces the number of stenosed vessels. It has been shown in many studies of medically treated patients with angiographically proven coronary disease (including the medical group of the V.A. Cooperation study) that late mortality increases with the number of significant coronary lesions present and the magnitude of impairment of left ventricular function.[4,6,19] One vessel disease with normal ventricular function has been associated with late attrition rates of about 2–3% while two vessel disease carried 3–6% and three vessel disease is associated with an attrition of around 10% *per annum.*

Examination of Table 11 and Figure 3 indicate that following operation, patients with normal ventricular function have similar late attrition rates regardless of the number of vessels diseased preoperatively and that survival is essentially normal at five years. The main difference in survival among subgroups was due to the increased perioperative mortality in patients with multivessel disease, a difference that is minimal in our current experience.

Similarly, if the patients are grouped according to the degree of revascularization achieved and thus the number of significant residual lesions present, it can be seen from Table 7 that the best survival was obtained in patients with no residual lesions while patients with one or two residual lesions had depressed survival rates regardless of the number of preoperative lesions. A similar but more pronounced pattern of survival is seen in those patients with poor ventricular function. However, although the bypass operation may improve advanced ventricular dysfunction in some cases,[14] (and unpublished data), it cannot correct it completely and so it is not surprising that survival in this group should remain depressed, although better than that reported in medical series.

We have reported previously upon the fate of these patients beyond five years in regard to their sustained symptomatic relief and enduringly good functional rehabilitation.[7] We feel that this data, combined with the good late survival rates we have obtained subsequently suggest that it is rare for a patient to require more than three grafts to achieve a good result. The current fashion for multiple grafts (up to eight to nine per patient) is unsupported by any conclusive published data as to its benefit. Furthermore, the long-term patency of grafts attached to very small secondary

TABLE 12. *Comparison of Surgical Results of V.A. Cooperative Study and B.C.M. Series*

	VA 1972–74	BCM 1968–71	BCM 1971–72
Operative mortality	5.6%	5.5%	3.8%
No. grafts/patient	1.9	1.5	1.8
Graft patency rate	69%	90.5%	84.3%
No. of patients with no grafts patent	12%	2.6%	7.4%
No. of patients with all grafts patent	54%	85.9%	74.1%
Crude survival at 36 months	88%	85.0%	92.2%
Overall average crude annual attrition rate	4.0%	5.0%	2.6%
Crude average annual attrition rate (excluding operative mortality)	2.3%	3.1%	1.3%

and tertiary coronary branches remains unknown. In addition, our previous studies indicate that stenoses of <50% rarely progress making prophylactic grafts unnecessary.[7]

It is apparent from a comparison of the initial and subsequent experience (Table 6) that the combination of an adequate number of grafts per patient (up to three grafts) and good graft patency produces a group of patients with a very low incidence of significant residual disease. We believe that this is why the late annual attrition rate in our later series was reduced by over 50% from the 3.1% of the earlier experience to 1.3% and why our results are better than the 2.3% *per annum* of the V.A. Cooperative study (Table 12). With only 54% of V.A. patients having all grafts patent, a significant number must have had residual two and three vessel disease.

It is not surprising, therefore, that the findings of the V.A. Cooperative study were that both medical and surgical patients had equal survival rates at 36 months.[18] It is important to note, however, that whereas the medical group has had a relatively constant annual attrition rate of 4% *per annum*, the surgical group, excluding an operative mortality of 5.6% had an annual attrition rate of only 2.3% *per annum*. This suggests that even in the V.A. study that at a longer follow-up interval the survival of the surgical group eventually will exceed that of the medical group. This has been the case in the Houston Veterans Administration study where the survival at four years in the surgical group was 88% compared with 79% in the medical group.[13]

Conclusion

We feel therefore, that the coronary bypass procedure is effective not only in the relief of symptoms but also in prolonging life. Comparison of late survival rates after operation with a highly selected good risk medical group indicate that the two year medical attrition is equal to the five year surgical attrition. Furthermore, in surgical patients with good left ventricular function, late survival is normal.

This study, however, does emphasize the importance of the technical quality of the coronary bypass operation performed. Improved survival will be observed only in those patients in whom an adequate number of patent grafts have been established at low operative risk. As is so graphically shown by the V.A. Cooperative study, this significant benefit will be denied to patients in whom an inadequate surgical result has been obtained.

As the technical quality of coronary bypass surgery is so readily determined by examination of the operative mortality, perioperative infarction rate and graft patency rate, it is essential that the cardiologist and surgeon monitor the postoperative results to ensure a standard which will lead to enhanced survival in their patients as well as symptomatic relief.

References

1. Anderson, R. P., Rahimtoola, S. H., Bonchek, L. I., et al.: The Prognosis of Patients with Coronary Artery Disease After Coronary Bypass Operations—Time Related Progress of 532 Patients with Disabling Angina Pectoris. Circulation, 50:274, 1974.
2. Braunwald, E.: Editorial: Coronary-Artery Surgery at The Crossroads. N. Engl. J. Med., 297:661, 1977.
3. Brock, J.: Actuarial Director, Prudential Insurance Company, Houston, Texas. Personal Communication, 1977.
4. Bruschke, A. V. A., Proudfitt, W. L. and Sones, F. M., Jr.: Progress Study of 590 Consecutive Non-Surgical Cases of Coronary Disease Followed 5–9 Years. I. Arteriographic Correlations. Circulation, 47:1147, 1973.
5. Conley, M. J., Wechster, A. S. and Anderson, R. W.: The Relationship of Patient Selection to Prognosis Following Aortocoronary Bypass. Circulation, 55:158, 1977.
6. Detre, K., Hultgren, H. and Takaro, T.: Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III-Methods and Baseline Characteristics, Including Experience with Medical Treatment. Am. J. Cardiol., 40:212, 1977.
7. Lawrie, G. M., Morris, G. C., Jr., Howell, J. F., et al.: The Results of Coronary Bypass More Than Five Years After Operation in 434 Patients: Clinical, Exercise Treadmill and Angiographic Correlations. Am. J. Cardiol., 40:665, 1977.
8. Grondin, C. M.: Factors Influencing Graft Patency. Syllabus: The First Decade of Bypass Graft Surgery for Coronary Artery Disease. Cleveland Clinic Foundation, 1977, p. 75.
9. Lawrie, G. M., Morris, G. C., Jr., Chapman, D. W., et al.: Patterns of Patency of 596 Vein Grafts Up to Seven Years After Aorto-Coronary Bypass. J. Thorac. Cardiovasc. Surg., 73:443, 1977.
10. Lawrie, G. C., Lie, J. T., Morris, G. C., Jr., et al.: Vein Graft Patency and Intimal Proliferation After Aortocoronary Bypass: Early and Long-Term Angiopathologic Correlations. Am. J. Cardiol. 38:856, 1976.
11. Lie, J. T., Lawrie, G. M. and Morris, G. C., Jr.: Aortocoronary Bypass Saphenous Vein Graft Atherosclerosis: Anatomic Study of 99 Vein Grafts from Normal and Hyperlipoproteinemic Patients Up to 75 Months Post-operatively. Am. J. Cardiol., 40:906, 1977.
12. Mathur, V. S. and Guinn, G. A.: Prospective Randomized Study of Coronary Bypass Surgery in Stable Angina: The First Hundred Patients. Circulation 51, 52, Suppl. 1:133, 1975.
13. Mathur, V.: Personal Communication. 1977.
14. Morris, G. C., Jr.: Coronary artery surgery and congestive heart failure. *In* Norman, J. C., (ed.) Coronary Artery Medicine and Surgery: Concepts and Controversies New York, Appleton-Century Crofts, pp. 676–681, 1975.
15. Morris, G. C., Jr., Reul, G. J., Howell, J. F., et al.: Follow-up Results of Distal Coronary Artery Bypass for Ischemic Heart Disease. Am. J. Cardiol., 29:180, 1972.
16. Morris, G. C., Jr., Howell, J. F., Crawford, E. S., et al.: The Distal Coronary Bypass. Ann. Surg., 172:652, 1970.
17. Mundth, E. D. and Austen, W. G.: Surgical Measures for Coronary Heart Disease (3 Parts). N. Engl. J. Med., 293: 13, 75–80, 124–130, 1975.
18. Murphy, M. L., Hultgren, H. N., Detre, K., et al.: Treatment of Chronic Stable Angina: A Preliminary Report of Survival Data of the Randomized Veterans Administration Cooperative Study. N. Engl. J. Med., 297:621, 1977.
19. Oberman, A., Jones, W. B., Riley, C. P., et al.: Natural History of Coronary Artery Disease. Bull. N.Y. Acad. Med., 48: 1109, 1972.

20. Read, R. C., Murphy, M. L., Hultgren, H. N., et al. Survival of Men Treated for Chronic Stable Angina Pectoris. J. Thorac. Cardiovasc. Surg. 75:1, 1978.
21. Scheidt, S.: Unstable Angina: Medical Management or Surgery. Cardiovasc. Med., 2:541, 1977.
22. Sheldon, W. C.: Factors Influencing Patency of Coronary Bypass Grafts. Syllabus: The First Decade of Bypass Graft Surgery for Coronary Artery Disease. Cleveland Clinic Foundation 1977, pp. 77–79.
23. Sheldon, W. C., Rincon, G., Effler, D. B., et al.: Vein Graft Surgery for Coronary Artery Disease—Surgical and Angiographic Results in 1000 Patients. Circulation, 47, Suppl. 3:184, 1973.
24. Takaro, T. Hultgren, H. N., Lipton, M. J., et al.: The V.A. Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease II: Subgroup with Significant Left Main Lesions. Circulation 54, Suppl. 3:107–117, 1976.

DISCUSSION

DR. DUNCAN A. KILLEN (Kansas City, Missouri): I would like to comment relative to each paper. I would like to show data that I think confirm the data that the authors have presented, and our conclusions, I think, are very similar.

(Slide) This relates to the treatment of patients with left main coronary artery occlusions, or partial occlusions. At the St. Luke's Hospital in Kansas City we have treated 270 such patients from 1971 through 1976, and this represents approximately 10% of our experience with isolated coronary artery bypass patients. We have followed these patients, and these are the number of patients alive at follow-up. As you see, beyond three years we really do not have a very large group of patients followed, but the survival curve—and this includes the operative mortality—at five years is 92%. And as mentioned earlier, this is comparable to the survival of the average U. S. citizen matched for age and sex. I think this is something that is very important. Otherwise, patients selected for operation (and admittedly, all patients are not operated on) have a survival which is equivalent to that of the average population.

Now, if you look at the medically treated group, we go back to the series reported a long time ago from the Cleveland Clinic, showing the overall survival of patients with similar lesions, and this curve represents the VA study which has been referred to earlier. These patients are from a randomized study. Otherwise, these patients are candidates for surgery, and were not operated on. And I believe that from the data that we have heard presented this morning we have seen enough randomized studies of left main lesions. I think it's clear that surgery is indicated in this group, and I think that is becoming general opinion in the cardiologists' minds as well.

(Slide) I would like to speak to the long-term follow-up of all patients with coronary artery disease undergoing operation. We have recently followed up 282 patients that were operated on at least five years previously, and we were able to get follow-up on all of these patients to the time of death or for at least five years. We have surveyed them according to the course of their angina, and as you can see, there has been deterioration in their angina status, and at five years only 57% remain angina free. And I think this is what we would anticipate. Coronary artery disease is a progressive disease. They have certainly not reverted to their preoperative status, but there is deterioration, and, of course, some of these patients have required reoperation during this period of time.

(Slide) And the last slide that I would like to show is the survival of these initial 282 patients; and again, this includes the operative mortality. And at five years the patient survival was 86.9%; and above it is the survival of the average population, matched for age and sex. Approximately 60% of these patients had three vessel disease. We have since, of course, extended this series, and extended the follow-up. In the follow-up of the first 2000 patients operated on 1971 through 1976, we have found that the survival curve has shifted upward somewhat, and the projected survival, using the life table method, is 90%, which is equivalent, essentially, to the population, when matched for sex and age.

DR. THOMAS L. KILGORE, JR. (Jackson, Mississippi): Drs. Morris and Lawrie's presentation is in rebuttal to the widely publicized VA report with which you are all familiar. I would like to present some observations on a group of 321 of our patients having coronary surgery and followed for a mean of four years, in hopes of emphasizing the conclusions that Drs. Lawrie and Morris have presented.

(Slide) These few slides compare the actuarial survival curves of our surgical series, shown in yellow, with that of a group of patients receiving medical therapy alone, as previously reported by Dr. Joseph Reeves and associates, shown in orange. Cardiac as well as noncardiac late deaths were included in both the surgical and medical series. Operative deaths also entered these curves.

Forty-eight per cent of our 321 patients received two grafts, though some had other vessels that were diseased but not bypassable. We observed a 3% annual mortality, compared to the 7% rate seen in the medical series with two vessel disease.

Thirty-eight per cent of the series received three or more grafts, and the annual mortality was 2%, while the medical series of three vessel disease died at a rate of 12% per year.

In the overall surgical series, the operative mortality was 2.4%, and the survival at four years was just under 90%, whereas only about 82% of the medical series were alive at the end of two years.

I would point out that the VA study excluded those patients with unstable angina, while patients with that syndrome were included in both the medical and surgical series shown here.

The authors' observations present convincing arguments in favor of the superiority of surgical management versus medical therapy alone, and my own experience leads me to agree with their conclusions.

In closing, I would like to ask Dr. Morris if any patients in his series have had recurrence of angina after initial improvement; and if so, what percentage of them were considered as candidates for reoperation?

DR. CHARLES R. HATCHER, JR. (Atlanta, Georgia): I think that Dr. Morris' paper is exactly the type of data that is required to put the medical/surgical therapy controversy, based on the VA cooperative study, in proper perspective.

I especially wish to emphasize our agreement with the conclusions that the determinants of survival are essentially two: the status of ventricular function preoperatively, and the quality of the surgery.

The quality of the surgery, of course, can be easily defined through the parameters of operative mortality, vein patency rate, perioperative infarction rate, and completeness of revascularization.

It is a bit unfortunate that just at the time that the quality of surgery has reached such a pinnacle of success, the value of the operation should be brought into question. I realize that the VA researchers did not mean this to occur, but they took a very limited group of patients with excellent ventricular function, at minimum risk, and then compared the short-term survival rates of the medical versus the surgical group. The lay press and others have taken that basic comment and extrapolated it to cover many subsets of coronary artery disease.

I would like to make the plea that at the present time, based on the fact that we have figures such as Dr. Morris' to give us the confidence that the long-term survival is going to be excellent, and with data accumulating showing that the quality of surgery is outstanding, we continue to expand the role of surgery in the treatment of coronary artery disease.

(Slide) Before leaving Atlanta, I pulled from our computerized data collection system the last 1000 patients operated upon for coronary artery disease with bypass surgery. This represented a 15 month experience, and during that time the hospital mortality was 1%, and the perioperative infarction rate 5%. The graft patency rate of 90% is based on those restudies performed over the last three years. These results are quite typical of the results that are being achieved by members of this Association in many surgical centers.

(Slide) To comment on left main disease, I would say that there is no question in anyone's mind at the present time that left main disease should be treated surgically rather than medically. This is a short follow-up, to be sure, but in 180 patients seen with left main disease at Emory, 138 were operated upon, and 24 months later 85% were alive, whereas the medical service, in not operating on 47, had a mortality of 43%.

Similarly, if we limit our application of surgery to severe obstruction and/or significant left ventricular dysfunction, as defined here by ejection fractions below 35 and LVEDP's greater than 20, or take a group in whom both the LAD and the right coronary artery were totally occluded, we find that even there the operative mortality is quite low, and that the follow-up is quite satisfactory.

Even in advanced disease, realizing that these patients will not have the good outlook of those with excellent ventricular function, the results are sufficiently good to warrant application of surgery without question.

And, finally, those patients who have not had a satisfactory course following acute myocardial infarction may on occasion be operated upon with dramatic benefit. We recently reviewed a group of 35 patients operated upon and divided into these groups, ten operated on within 24 hours of acute myocardial infarction, nine within two to seven days of acute myocardial infarction, and 16 patients operated on from eight days to one month of acute myocardial infarction. These are patients who had certain complications that required surgical intervention.

The hospital mortality was 0 in that group of 35 patients, and we have lost none to follow-up, albeit the follow-up is quite short. 68% were completely relieved of angina, 26% improved, and 6% were either unchanged or worse. Seventeen of those 35 patients have been restudied for graft patency. In that group all grafts were present in 76%.

Dr. Frank C. Spencer (New York, New York): (Slide) First, I want to emphasize two basic facts about coronary disease, which I briefly alluded to on Monday. It causes about 600,000 deaths in this country annually. This large number accounts for more than one-half of all deaths in the American male each year from all causes combined. This alarmingly high figure itself, which has been true for many years, automatically raises serious questions about the efficacy of non-operation therapy in many patients because most of the present forms of medical therapy have been available for the last 10–20 years.

The second point not widely appreciated is that to date, only two factors have been proved to influence the death rate: avoiding cigarette smoking and controlling hypertension. Other forms of medical therapy, including limitation of lipid intake, betablockers, weight reductions, and jogging, are all reasonable but are actually even more unproven on influencing coronary disease than coronary bypass. Hence, the debate about the indications for coronary bypass is not one of comparing a proved form of therapy with a new form of surgical therapy, but the more basic one of proving the benefit of both forms of therapy presently employed.

(Slide) One reason for the confusion in data is the wide variability in atherosclerosis, ranging from the very mild to the very lethal. This variation in itself is due to the interplay of two opposing factors: How rapidly the disease progresses versus how rapidly the collaterals develop. Unfortunately, at the present, our efforts are very limited in influencing either one of these two processes, progression of atherosclerosis or growth of collateral circulation. Hence, there is a very wide spectrum in coronary disease and the importance in all studies is to compare comparable groups.

The disease is similar to atherosclerosis in the femoral artery. Few would advocate bypass grafting whose only symptom was claudication after walking eight to ten blocks, for abundant data indicate that the risk of gangrene within five years is very small. By contrast, no one would argue about bypass grafting for someone with rest pain, dependent rubor, and early ulceration, where amputation will surely become necessary unless operation is done.

(Slide) Our data from New York University were presented at the Toronto Meeting of the American Association for Thoracic Surgery last April. A 98% follow-up of our total experiences at New York University with elective bypass operations, including over 1100 patients over a period of about seven years, found that 88% were alive five years later.

In analyzing this slide in detail, the overall mortality for the five year period was 5%, decreasing to the range of about 2% in the last few years. For the overall group of each 100 patients operated upon, 95 left the hospital. Five years later, 88 were alive, with seven dying during the period of five years, an average annual mortality of only 1.4%.

A second surprising point from this actuarial curve is that the slope of the curve is even. One would predict that if the grafts closed, or the atherosclerosis progressed rapidly, the curve should progressively change with an increasing mortality rate three to five years later. A second important point is that the slope of this actuarial survival curve exactly parallels that for a similar matched population of age and sex, indicating that operation had a very strong beneficial influence on longevity. Not mentioned, this is even more remarkable because the majority of these patients were seriously disabled with their disease and were operated upon after attempts at all available medical therapy had failed.

(Slide) This slide shows similar figures from the Ochsner Clinic, given at one of our national vascular meetings last summer in Rochester, New York, showing a five year survival near 90% in a series of about 1000 patients.

The similarity of our results and those from the Ochsner Clinic with the results reported by Drs. Morris and Lawrie is striking. I would like to emphasize several points.

First, 670 of their patients have been followed for over five years and angiograms performed on 105 of these. At five years, the vein graft patency rate was 89% and over 96% had one patent graft. To my knowledge, these are the best long-term data about graft patency ever published. Hence, one of the major questions about coronary bypass answered in this study is that patency for at least 5 years of the vein grafts is probably in the majority of patients.

Their survival rate ranges 81–92%, varying with ventricular function, a factor well known to have a strong influence on longevity. I had the opportunity of reading the manuscript in detail and would recommend its close study by all working in this area.

In closing, I have several questions: 1) What are your current indications for operation, severity of angina or the degree of obstruction on the angiogram? More specifically, would you recommend bypass on a patient with asymptomatic triple vessel disease on the angiogram? 2) What is your present technique of bypass, has it been modified with experience, and what is the frequency of myocardial infarction following bypass? 3) Finally, with the great concern about cost of medical care, what percentage of your patients are working?

Dr. Gilbert S. Campbell (Little Rock, Arkansas): Cruelty to animals is abhorrent to most of us. In the discussion thus far the Veterans Administration Trial (randomized prospective study on the treatment of a well defined group of patients with coronary artery disease) has been kicked around like a rejected mongrel dog. Perhaps some kicks are deserved, but all the kickers may not be flawless in their clairvoyance.

Dr. Timothy Takaro headed the surgical section of the Veterans Administration study. I am pleased that the Little Rock VA Hospital put more patients into the study than any other hospital. The surgical procedures were done by Drs. Raymond C. Read and

G. Doyne Williams. The quality of the surgery was not contaminated by my expertise so I can speak objectively.

The VA study has evoked a visceral rather than a cerebral response in many surgeons and cardiologists. The VA Trial may or may not tarnish the golden egg of coronary artery surgery but at least some have asked "Is it solid gold?"

I'm not questioning the beautiful papers presented here, but I do know that in some locations if a person has a little dyspepsia and grabs his chest, he may have a skip graft. Now if that doesn't help him, he may be subjected to a careful history and physical examination.

Dr. Frank Spencer's comments were right to the point. Lipid lowering has been proven ineffective to date with diet and/or drugs. The best handle to date on lipid lowering is a surgical handle—distal ileal bypass described by Drs. Henry Buchwald and Richard Varco. At the University of Arkansas, we're a very small part of a scientific, prospective, randomized study on the surgical control of hyperlipidemia. It is hoped that in the years ahead we will have 1000 patients, 500 randomized to the ileal bypass (which drops lipids 40–45%) and 500 control patients. It's the only operation that I'm aware of that gets at the metabolic cause of atherosclerosis.

A major league ball player with coronary artery occlusion did not have a skip graft but had the distal ileum (the distal one third) bypassed by Dr. Buchwald at the University of Minnesota. Subsequent arteriography showed some resolution of the obstructive lesions in the coronary arteries. It is the only operation that attacks what may very well be the cause of these lesions and hopefully the Minnesota based study will provide a definitive answer to the lipid-atherosclerosis hypothesis.

Dr. William C. Alford, Jr. (Closing discussion): I am indebted to Dr. Killen for presenting his figures, primarily because his results are better than ours. I believe they have the lowest operative mortality and best long-term follow-up of any group that I know of, and I'm trying to do as well.

We think this study has shown that in the left main group—which even Dr. Campbell doesn't question—coronary artery bypass is effective in increasing survival over the non-operated group. The operation was not designed for that, as you know. It was designed to relieve angina, and, as Dr. Hatcher has shown, it is most effective in that particular aspect.

However, if coronary bypass for left main coronary disease can be accepted as increasing survival, then perhaps it should be looked at more critically in all significantly ill patients with the same disease.

Dr. Gerald M. Lawrie (Closing discussion):

I must say, I feel something like a fox let loose in a henhouse, after all these discussions, with so many things to answer. Perhaps if I could show some slides to give the perspective from which our current attitudes have developed.

(Slide) We are conducting an on-going follow-up of a large group of patients, all operated on more than five years ago. Because we have had the opportunity to review all the patients more than five years after operation, the actuarial technique of analysis becomes redundant, because every patient has been followed through the entire interval of five years.

This is a consecutive series of 1108 patients operated on by Dr. Morris and Dr. Howell at Baylor College of Medicine between 1971 and 1972. It includes left main disease, and includes patients with impaired left ventricular function including those who had left ventricular aneurysmectomy.

No patient has been excluded because of poor ventricular function. And, in fact, at that time there was considerable interest in surgery for congestive heart failure, so a number of patients had quite severe congestive heart failure.

The overall survival in this group, operated between 1971 and 1972, was 90.7%. This is far superior to the medical and surgical results of the VA Cooperative study, which was a far more highly selected group of patients. Our results now are superior to these particularly in relation to operative mortality and the degree of revascularization achieved.

A curve of survival for a normal population was prepared for us by the actuarial director of Prudential Insurance Company from the age and sex of every one of these patients—it is an exact matched curve. The normal survival was 92.7%.

If we look now at patients with an end diastolic pressure of less than 15 mm of mercury, and no discrete akinetic or aneurysmal area of left ventricle (and we define these patients as having good left ventricular function; not normal, because many of these had dilated ventricles and impaired ejection fractions, but we did not use this to classify them) simply these two objective parameters.

We can see that the survival in this group of patients is actually superior to normal beyond five years; and once again, superior to the VA study.

Now, looking at the survival of the various subgroups in more detail, the unbroken lines are the patients with good left ventricular function, and the broken lines, are the patients with poor ventricular function, as we have defined these terms.

It is apparent that successful revascularization has eliminated the difference in survival of patients beyond five years regardless of the preoperative extent of their coronary artery disease. In other words, all these patients, including single, double, triple and left main disease, have ended up with comparable survival, and all those patients with good left ventricular function have normal survival.

In other words, we feel that a functioning bypass does, in effect, eliminate the significance of a coronary artery lesion. In a recently published study, we examined graft function and progression of disease in considerable detail. It is not accurate to say that coronary artery disease is a relentlessly progressive disease. Less than 10% of these patients had significant progression over a five year period.

Coronary artery disease, like atherosclerosis elsewhere in the body, by and large, progresses at a slow rate. Of course, we do see a small number of patients with rapidly progressive disease, but by and large it is stable over five years.

Looking at the patients with poor ventricular function, their survival is far superior to any group of similar medically treated patients. And now we have found the reason why: since we have introduced the radioisotope ejection fraction studies (which have become available recently), it has become apparent that what we suspected clinically for many years but couldn't show—that coronary bypass improves ventricular function—is absolutely correct.

And we have now extended this even into the group of patients with poor ventricular function without angina. In selected patients, we have shown doubling of the ejection fraction postoperatively by radioisotope study. So the improved survival here can be attributed to revascularization of the impaired ventricle.

Of course, some of this impairment is irreversible, and so these people continue to have a depressed survival.

As we have continued to follow these patients, we have employed professional police investigators to pursue people to the ends of the earth, and we have now been able to obtain an almost 99% follow-up beyond five years.

We believe, therefore, that there is no question but that the coronary bypass operation restores people with good preoperative left ventricular function to normal, not improved, but normal life expectance. And we believe this has extremely important implications in the management of coronary artery disease.

We feel coronary disease is analogous to a malignancy. We're dealing with a malignant disease that will take life, and we can no longer tolerate patients being allowed to deteriorate into a state of ventricular function where surgery can no longer offer them the opportunity which they deserve to achieve a normal life expectancy. And I think this is something about which we need to educate our cardiological colleagues.

The other thing is, there is no need for any form of randomized prospective study in regard to normal ventricular function. What we now need is a medical series of angiographically similar patients who have achieved a normal five-year survival; and I sincerely doubt that this will be forthcoming.

I think, in answer to Dr. Campbell, none of us object to scientific endeavor, and I think all of us accept the VA Co-operative study as a very honest attempt to answer a difficult question. My own objection to it is the rather slanted editorial which accompanies the article, and which was communicated to the press in rather an exuberant fashion, and which has led to so much suffering among so many patients.

The other point which I think bears emphasis is that the claim in the body of the report itself that the quality of surgery achieved in the VA cooperative study was acceptable for 1972–1974 is just not acceptable. Neither the operative mortality in such a good-risk group of patients nor the graft patency achieved even approached that being achieved by many large centers prior to 1972, as we have demonstrated.

In answer to Dr. Kilgore, we have had to reoperate on a small number of patients. The most common reason has been an inadequate initial operation. And as you saw in our presentation, a number of patients between 1968 to 1971 had too few grafts placed. Also, when we reviewed some of the early arteriograms, we found that we had been underinterpreting disease quite consistently at that time. So the most common reason has been either unoperated lesions which were there all the time or lesions which have progressed, and, infrequently, graft occlusion.

We have been very interested in the grafts, and we have studied them both angiographically and histologically beyond five years. We have reported in some detail on the role of intimal proliferation in graft patency and we have published another article on graft atherosclerosis, which is rarely of significance.

In answer to Dr. Spencer, we did not exclude patients with hypertension. We did list the exclusions of the VA study. I'm sorry we didn't get the manuscript to you sooner, but the federal government has been taking an active role in inhibiting coronary bypass, and we suspect the U.S. Postal Service has been enlisted to further this end.

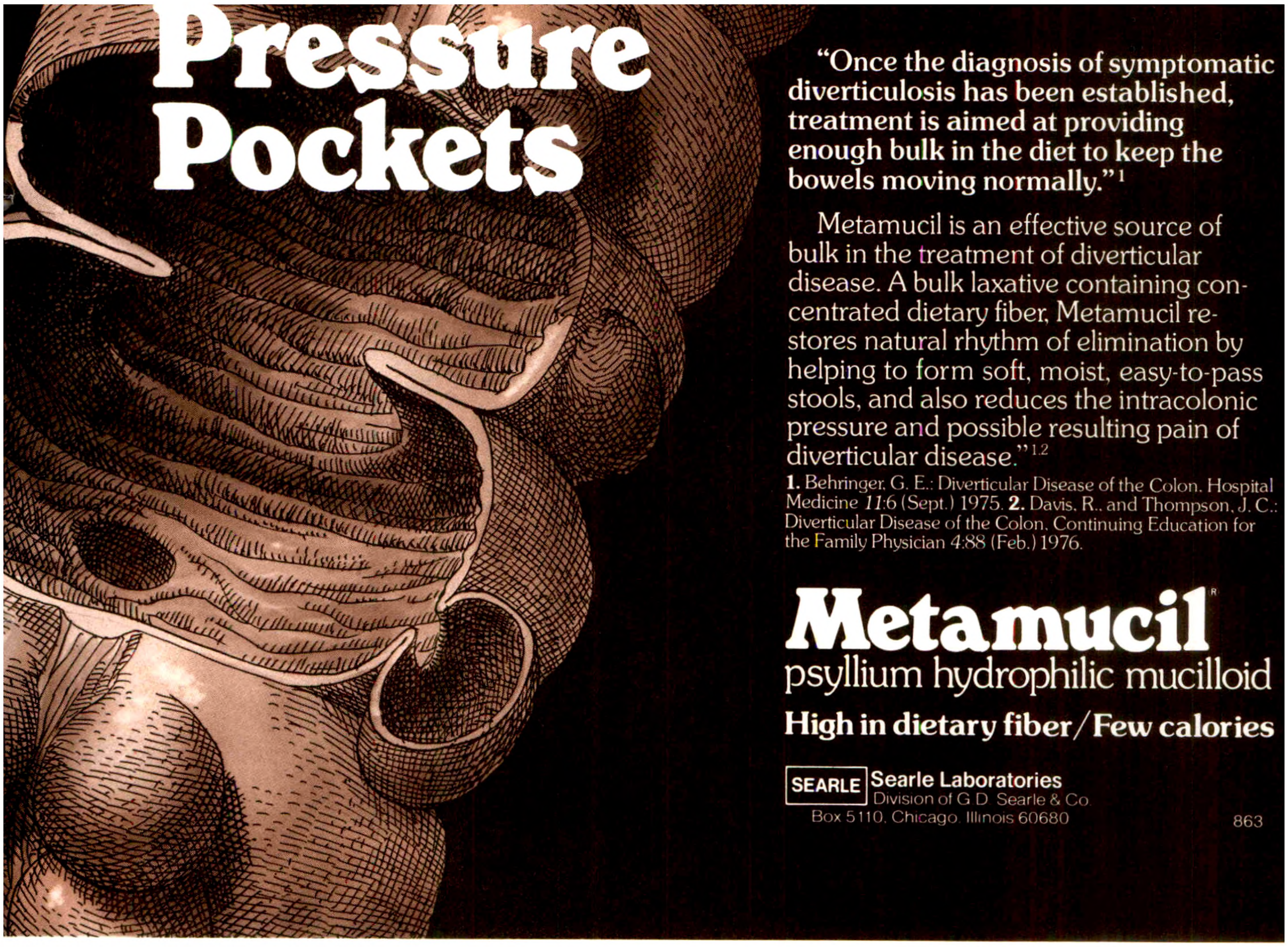
Now, as to indications for operation, angina pectoris remains our principal indication for investigation. Since we have obtained the results of these long term studies we have become more aggressive in offering operation to people with double and triple vessel disease, as well as left main disease, on the basis of anatomy alone: because our data tells us that these people can be restored to a normal life expectancy.

Our early interest in the management of congestive heart failure without angina has been rekindled by the recent advent of the thallium scans, and the ability to measure ejection fraction changes preoperatively in response to nitroglycerin. Using this technique, we have identified a subgroup of patients with congestive heart failure, and we have been able to demonstrate an increased ejection fraction postoperatively.

Our most common technique remains a single period of normothermic ischemic arrest. Our perioperative infarction rate remains 4%. The interval infarction rates remained steady at about 3½ to 4% *per annum*. Analysis of our data suggests to us that there are subgroups of patients who probably will benefit from some form of myocardial preservation, and we are initiating studies using isotope ejection fraction measurements to evaluate the role of the various cardioplegic solutions in these higher risk patients. But for the average patient with good ventricular function, we continue to use normothermic ischemic arrest.

In our long-term follow-up, over 80% of our patients are working. Symptomatic relief remains constant at over 90%.

We feel, therefore, that the coronary bypass is an ideal treatment for angina pectoris, and our long-term studies, clinical, angiographic, and pathologic, indicate to us that through five years at least the results are extremely durable.



"Once the diagnosis of symptomatic diverticulosis has been established, treatment is aimed at providing enough bulk in the diet to keep the bowels moving normally."[1]

Metamucil is an effective source of bulk in the treatment of diverticular disease. A bulk laxative containing concentrated dietary fiber, Metamucil restores natural rhythm of elimination by helping to form soft, moist, easy-to-pass stools, and also reduces the intracolonic pressure and possible resulting pain of diverticular disease."[1,2]

1. Behringer, G. E.: Diverticular Disease of the Colon, Hospital Medicine *11*:6 (Sept.) 1975. **2.** Davis, R., and Thompson, J. C.: Diverticular Disease of the Colon, Continuing Education for the Family Physician 4:88 (Feb.) 1976.

Metamucil®
psyllium hydrophilic mucilloid

High in dietary fiber/Few calories

SEARLE **Searle Laboratories**
Division of G.D. Searle & Co.
Box 5110, Chicago, Illinois 60680

863

Complications
in Vascular Surgery

***Edited by* HUGH G. BEEBE, M.D.,**
With 18 Contributors.

Outstanding vascular surgeons from all sections of the country have pooled their composite experience and knowledge for this in-depth work. Each has written on a specific vascular complication and gives you the benefit of his expertise in this area. Three objectives are always in view: 1) To help you prevent complications where the causes are known and can be anticipated. 2) To provide you with a clear guide to the management of complications. 3) To establish a foundation of information from which you can deal logically and effectively with problems not described. This work reaps the benefit of significant appraisals of long-term follow-up studies that became possible during the last ten years.

402 Pages • 175 Illustrations • 1973 • $28.00

J. B. LIPPINCOTT CO.
East Washington Square, Phila., Pa. 19105

Please send me:

Complications
in Vascular Surgery $28.00

☐ Payment Enclosed ☐ Charge and Bill me

Name ________________

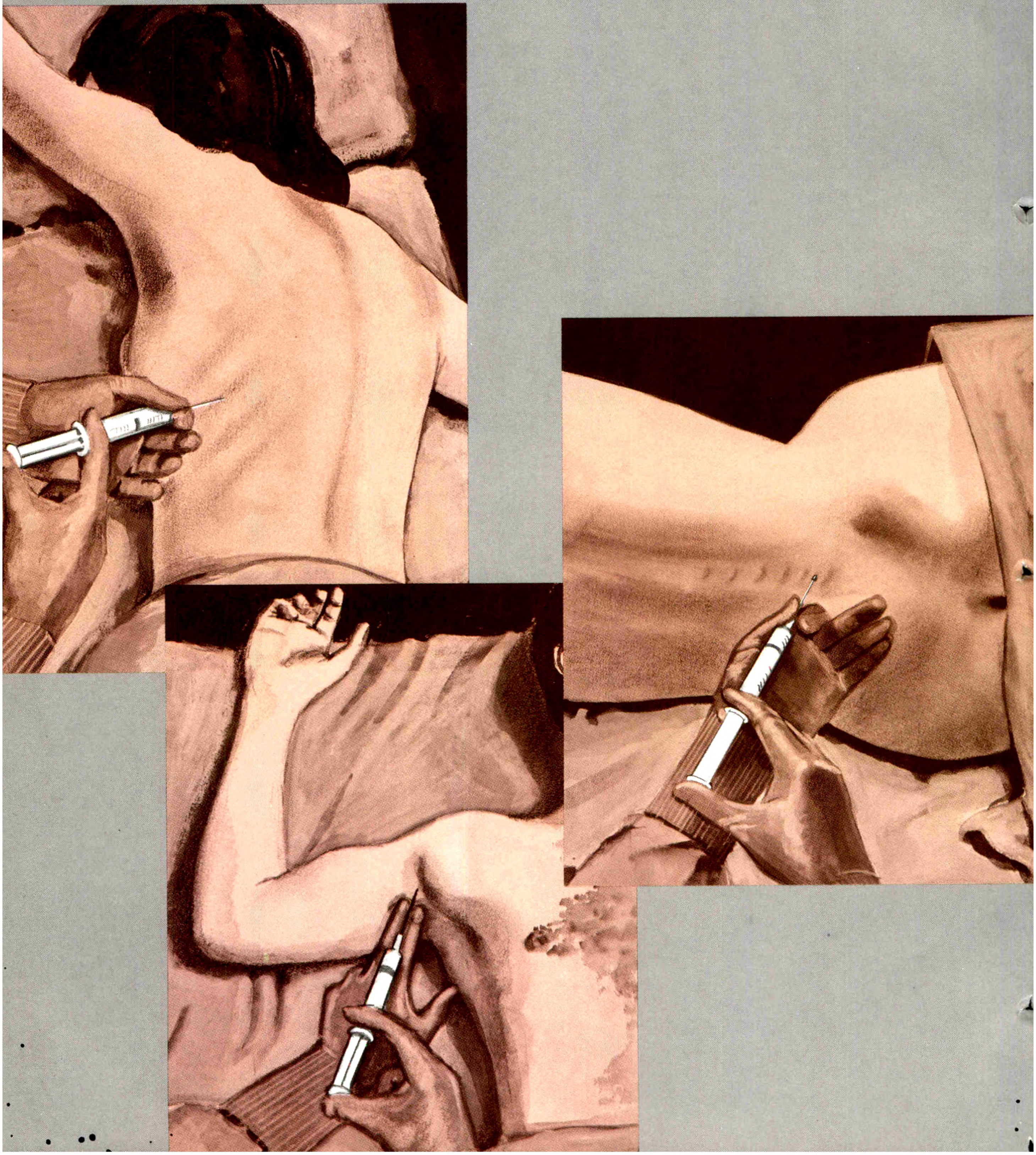
Address ________________

________________ Zip ________

AS 6/78

Lippincott

If you're using **Marcaine**®
brand of
bupivacaine hydrochloride
only because
of its prolonged action...



[redacted]you'r[redacted] mi[redacted]ing thr[redacted] other important reasons.

1. More control of motor block

The variety of Marcaine dosage strengths and the ability of Marcaine to provide complete sensory block *with* or *without* significant motor block gives you more control during surgical procedures.[1]

2. Less need for postoperative analgesics

Marcaine with or without epinephrine has been demonstrated to postpone or reduce significantly the need for postoperative narcotics.[1,2]
Results vary with the procedure and the dose administered.

3. Greater postoperative patient mobility

Of 20 patients with flank incision, half were given intraoperative bupivacaine (Marcaine) intercostal blocks. Those who were given Marcaine required less pain medication, were sitting up 2 days earlier, walking 3 days earlier, and took a regular diet 2 days sooner.[3] Ability to cough and breathe deeply was also greater in the Marcaine patients.[3]

The local anesthetic with more reasons to use it than any other.

Marcaine® hydrochloride
brand of
bupivacaine hydrochloride with or without epinephrine 1:200,000

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on the next page. As with any local anesthetic, inadvertent intravascular injection may result in general convulsions.

Please see following page for full prescribing information.

Marcaine® hydrochloride

brand of

bupivacaine hydrochloride

with or without epinephrine 1:200,000

The long-acting local anesthetic that gives you:

1. **More Control of Motor Block**
2. **Less Need for Postoperative Analgesics**
3. **Greater Postoperative Patient Mobility**

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References: 1. Moore DC, Bridenbaugh LD, Thompson GE, et al: Bupivacaine: a review of 11,080 cases. *Anesth Analg* 57: 42-53, 1978. **2.** Lund PC, Cwik JC, Vallesteros F: Bupivacaine—a new, long-acting local anesthetic agent: a preliminary clinical and laboratory report. *Anesth Analg* 49:103-114, 1970. **3.** Noller DW, Gillenwater JY, Howards SS, et al: Intercostal nerve block with flank incision. *J Urol* 117: 759-761, 1977.

BREON BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

FORMULA

PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl) %	mg./ml.	Epinephrine* (as bitartrate) Dilution	Methylparaben mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.50	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.50	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	0.5	.001	2	.0017	0.1
0.75	7.5	—	Not Available in Vials						—	—	—	—	—
0.75	7.5	1:200,000							0.5	.001	2	.0017	0.1

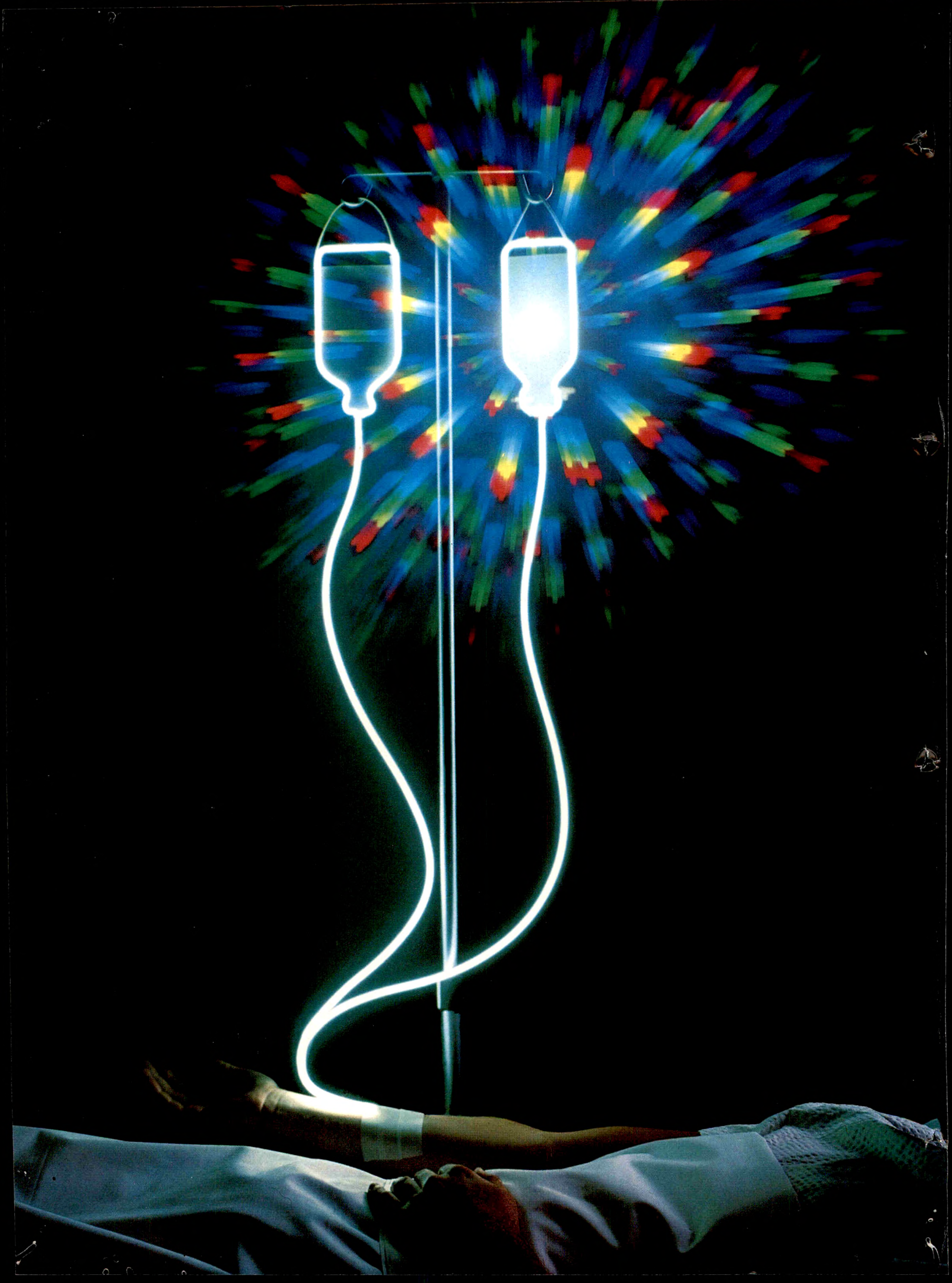
Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

Total
renter
utritio

Now
ssible v
pheral



Intralipid® 10% I.V. Fat Emulsion

Before the availability of Intralipid 10% I.V. Fat Emulsion, hyperalimentation was the only method of administering highly concentrated solutions of calories and nutrients. But hyperalimentation requires central venous catheterization, with all its attendant risks.

Now, with Intralipid 10% I.V. Fat Emulsion, there is an alternative — the lipid system of total parenteral nutrition. The lipid system consists of Intralipid 10% I.V. Fat Emulsion in conjunction with glucose, amino acids, electrolytes, minerals and vitamins, and provides all essential nutrients, including fat*, and adequate calories, via peripheral vein.

Intralipid 10% I.V. Fat Emulsion is a highly concentrated source of calories, providing 1.1 Calories per ml in an isotonic solution.

And because the lipid system includes fat in the I.V. nutritional regimen, Intralipid 10% I.V. Fat Emulsion attains the goal of balanced I.V. nutrition and prevents or corrects the symptoms of essential fatty acid deficiency.

Intralipid 10% I.V. Fat Emulsion also allows for balanced I.V. nutrition via central vein in those patients who require larger amounts of calories than can be supplied by peripheral infusion, or who have peripheral veins unsuitable for parenteral feeding. Central vein infusion of Intralipid 10% I.V. Fat Emulsion, with other nutrients infused separately can decrease the risk of metabolic disorders often encountered with hyperalimentation infusions — including osmotic diuresis, hyperglycemia, rebound hypoglycemia, hyperosmolar non-ketotic dehydration — and prevents or corrects essential fatty acid deficiency.

Intralipid 10% I.V. Fat Emulsion — could make the lipid system your method of choice in I.V. nutrition.

Now possible. Total parenteral nutrition via peripheral vein.

---

*Intralipid 10% I.V. Fat Emulsion must not be mixed with electrolyte or other nutrient solutions in order to avoid disturbing the stability of the emulsion. Filters must not be used with Intralipid 10% I.V. Fat Emulsion.

See following page for full prescribing information.

Intralipid® 10% I.V. Fat Emulsion

DESCRIPTION

Intralipid® 10% (10% Intravenous Fat Emulsion) is a fat emulsion prepared for intravenous administration. It is made up of 10% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and Water for Injection. In addition, Sodium Hydroxide has been added to adjust the pH to between 5.5 and 9.0.

The soybean oil is a refined natural product consisting of a mixture of neutral triglycerides of predominantly unsaturated fatty acids. The major component fatty acids are linoleic (54%), oleic (26%), palmitic (9%) and linolenic (8%).

Intralipid® 10% (10% Intravenous Fat Emulsion) has an osmolarity of approximately 280mOsm/liter and contains emulsified fat particles of approximately 0.5 micron size.

The total caloric value, including fat, phospholipid and glycerol, is 1.1 calories per ml. of Intralipid® 10% (10% Intravenous Fat Emulsion).

ACTIONS

Intralipid® 10% (10% Intravenous Fat Emulsion) is metabolized and utilized as a source of energy causing an increase in heat production, decrease in respiratory quotient and increase in oxygen consumption following its administration. The infused fat particles are cleared from the blood stream in a manner thought to be comparable to the clearing of chylomicrons.

Intralipid® 10% (10% Intravenous Fat Emulsion) will prevent the biochemical lesions of essential fatty acid deficiency (EFAD), and correct the clinical manifestations of the EFAD syndrome.

INDICATIONS

Intralipid® 10% (10% Intravenous Fat Emulsion) is indicated as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than five days) and as a source of essential fatty acids when a deficiency occurs.

CONTRAINDICATIONS

The administration of Intralipid® 10% (10% Intravenous Fat Emulsion) is contraindicated in patients with a disturbance of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis and acute pancreatitis if accompanied by hyperlipemia.

Intralipid® 10% (10% Intravenous Fat Emulsion) must not be mixed with electrolyte or other nutrient solutions; no additives can be placed in the bottle of Intralipid® 10%. It is supplied in single dose containers; a partly used bottle must not be stored for later use.

Filters should not be used with Intralipid® 10% (10% Intravenous Fat Emulsion).

Do not use any bottle in which there appears to be an oiling out of the emulsion.

WARNINGS

Caution should be exercised in administering Intralipid® 10% (10% Intravenous Fat Emulsion) to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders, or when there is danger of fat embolism.

PRECAUTIONS

When Intralipid® 10% (10% Intravenous Fat Emulsion) is administered, the patient's capacity to eliminate the infused fat from the circulation must be monitored. The lipemia must clear between daily infusions.

During long term intravenous nutrition with Intralipid® 10% (10% Intravenous Fat Emulsion), liver function tests should be performed; and if these tests indicate that liver function is impaired, the therapy should be withdrawn.

Frequent (some advise daily) platelet counts should be done in neonatal patients receiving parenteral nutrition with Intralipid® 10% (10% Intravenous Fat Emulsion).

Cutter Medical
Division of Cutter Laboratories, Inc.
Berkeley, California 94710

ADVERSE REACTIONS

The adverse reactions observed can be separated into two classes:

1. Those more frequently encountered which are due either to contamination of the intravenous catheter and result in sepsis, or to vein irritation by concurrently infused hypertonic solutions and may result in thrombophlebitis. These adverse reactions are inseparable from the hyperalimentation procedure with or without Intralipid® 10% (10% Intravenous Fat Emulsion); and
2. Those less frequent reactions more directly related to Intralipid® 10% (10% Intravenous Fat Emulsion) which are: a) **immediate or early adverse reactions**, each of which has been reported to occur, in clinical trials, in an incidence of less than 1%: dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness and irritation at the site of infusion, and rarely thrombocytopenia in neonates. b) **delayed adverse reactions:** hepatomegaly, splenomegaly, thrombocytopenia, leucopenia, transient increases in liver function tests, and over loading syndrome (focal seizures, fever, leukocytosis, splenomegaly and shock).

The deposition of a brown pigmentation in the reticuloendothelial system, the so-called "intravenous fat pigment", has been reported in patients infused with Intralipid® 10% (10% Intravenous Fat Emulsion). The cause and significance of this phenomenon are unknown.

DOSAGE AND ADMINISTRATION

Intralipid® 10% (10% Intravenous Fat Emulsion) should be administered as a part of total parenteral nutrition intravenously via a peripheral vein or by central venous infusion.

Adult Patients The initial rate of infusion in adults should be one ml./minute for the first 15 to 30 minutes of infusion. If no untoward reactions occur (see Adverse Reactions section), the infusion rate can be increased so that 500 ml. will be infused over a period of four hours. Only 500 ml. of Intralipid® 10% (10% Intravenous Fat Emulsion) should be infused into adults on the first day of therapy. If the patient has no untoward reactions, the dose can be increased on the following day. The daily dosage should not exceed 2.5 g./kg. of body weight. Intralipid® 10% should make up no more than 60% of the total caloric input of the patient. Carbohydrate and a source of amino acids should comprise the remaining 40% or more of the caloric input.

Pediatric Patients The initial rate of infusion in pediatric patients should be 0.1 ml./minute for the first 10 to 15 minutes. If no untoward reactions occur, the rate can be increased to permit infusion of 1 g./kg. in four hours. The daily dosage should not exceed 4 g./kg. of body weight. Intralipid® 10% (10% Intravenous Fat Emulsion) should make up no more than 60% of total caloric input of the patient. Carbohydrate and a source of amino acids should comprise the remaining 40% or more of the caloric input.

Fatty Acid Deficiency When Intralipid® 10% (10% Intravenous Fat Emulsion) is administered to correct fatty acid deficiency, eight to ten percent of the caloric input should be supplied by Intralipid® 10% in order to provide an adequate amount of linoleic acid to correct the deficiency.

Administration Intralipid® 10% (10% Intravenous Fat Emulsion) should be infused separately from any other intravenously administered solutions in order to avoid disturbing the stability of the emulsion. It must not be mixed with electrolyte or other nutrient solutions, and drugs or vitamins must not be added to the emulsion in the infusion bottle. It can be infused into the same peripheral vein as the carbohydrate-amino acids solution by means of a Y-connector located near the infusion site, and flow rates of each solution should be controlled separately by infusion pumps. Filters should not be used with Intralipid® 10% emulsion.

A special Intralipid® 10% (10% Intravenous Fat Emulsion) intravenous administration set is available.

Intralipid® 10% (10% Intravenous Fat Emulsion) is supplied in single dose containers; the remaining contents of a partly used bottle must not be stored for later use.

STORAGE

Intralipid® 10% should be stored under refrigeration at 4° to 8° C.

Do not freeze Intralipid® 10% (10% Intravenous Fat Emulsion); if accidentally frozen, discard bottle.

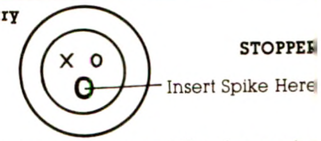
HOW SUPPLIED

Intralipid® 10% (10% Intravenous Fat Emulsion) is supplied as a sterile emulsion in 500 ml containers.

IMPORTANT
ADDITIONAL PRODUCT INFORMATION

Read Carefully Before Administration of Intralipid® I.V. Fat Emulsion

1. Stopper Entry



a. Be sure to swab the face of the stopper immediately before piercing.
b. Insert spike through the largest circle of prepared stopper with a straight thrust and then twist to fully seat spike.

2. Special Intralipid® I.V. Fat Emulsion Administration Set

A special Intralipid® I.V. Fat Emulsion administration set is provided with each bottle. Conventional administration sets contain polyvinyl chloride (PVC) components that contain DEH (Diethyl Hexyl Phthlate) as a plasticizer. Fat containing fluids such as Intralipid® extract DEH from these PVC components.

The special Intralipid® I.V. Fat Emulsion set does not contain DEHP. Therefore, this special [illegible] should be used for the administration of Intralipid® 10% (Intravenous Fat Emulsion).

Subject Index to Volume 187 (January-June 1978)

A

Abdomen, drainage, following appendectomy and cholecystectomy, 606
  peritonitis, experimental, intraperitoneal povidone-iodine in, 613
Adrenalectomy, with aminoglutethimide, in the management of post-menopausal patients with breast cancer, 478
Adriamycin, comparison of regional versus systemic chemotherapy with, 332
Albumin uptake, by skin, skeletal muscle and lung in living and dying patients, 31
Alcoholics, comparative survivals versus nonalcoholics after distal splenorenal shunt, 510
Aneurysm, abdominal aortic, rupture in inferior vena cava associated with horseshoe kidney, 329
  visceral artery, angiography as an aid in extra-enteric gastrointestinal bleeding due to, 357
Angiography, venous, surgical management of subcutaneous hemodialysis fistulas and, 194
Aorta, abdominal, extra-anatomic bypass of, 647
Appendix appendectomy, abdominal drainage following cholecystectomy and, 606
  appendicitis, in the elderly, 392
Artery(ies), anomalous subclavian, cause of dysphagia lusoria in children, 158
  aorta, abdominal, extra-anatomic bypass of, 647
  great surgery for transposition of in the first year of life, 143
  inferior mesenteric, stump pressure, 641
  left main coronary, surgical treatment of obstructive disease of, 658
  posterior gastric, incidence and surgical importance of, 134
  superior mesenteric, infusion of pitressin into, to control bleeding esophageal varices in cirrhotic patients, 337

B

Bleeding, extra-enteric gastrointestinal, angiography as an aid, in visceral artery aneurysm, 357
Blood, transfusion, impaction renal transplantation, 211
Blood flow, hepatofugal, in hepatic cirrhosis, 179
Breast, lesions, frozen section diagnosis of, 17
  reconstruction following mastectomy for cancer, 490
Burns, children recovering from, increased rates of whole body protein synthesis and breakdown in, 383
  thermal, lung water changes after, 288
Bypass, aortocoronary, prophylactic use of intra-aortic balloon pump in, for patients with left main coronary artery disease, 118
  coronary, late survival after, 665
  extra-anatomic, of the abdominal aorta, 647
  jejunoileal, effect on bile composition and the formation of biliary calculi, 57
  jejunoileal, prevention of bypass enteritis after, for morbid obesity, 502
Bypass enteritis, prevention after jejunoileal bypass for morbid obesity, 502

C

Catheterization, central venous, air embolism occurring as a complication, 375
Carcinoma, breast, adrenalectomy with aminoglutethimide in the management of postmenopausal patients with, 478
  breast, reconstruction following mastectomy, 490
  esophagus, resection and replacement for, 629
  gastric, following operation for peptic ulcer disease, 251
  large bowel, multiple of, 8
  large bowel, why operations fail, 549
  liposarcoma, retroperitoneal, 257
  lung, peripheral lymphocyte count as an aid in the clinical staging of, 248
  metastatic, dearterialization of the liver for, 38
  patients with, benign solitary lung lesions in, 241
  periampullary, endoscopic retrograde cholangiopancreatography in the diagnosis of, 313
Chemotherapy, regional versus systemic, with adriamycin, 332
Cholangiopancreatography, endoscopic retrograde, in the diagnosis of periampullary cancer, 313
Cholecystolithiasis, cholecystosonography for the diagnosis of, 465
Cholecystosonography, for the diagnosis of cholecystolithiasis, 465
Colon and Rectum, surgery of, systemic prophylaxis with doxycycline in, 362
Coma, hepatic, alterations in plasma and CSF amino acids, amines and metabolites in, 343

Cryopreservation, human parathyroid, 87
Cyst, congenital choledochal, management with intrahepatic involvement, 272
  splenic epidermoid, 231

D

Doxycycline, systemic prophylaxis with, in surgery of the colon and rectum, 362

E

Embolism, air, occurring as a complication of central venous catheterization, 375
  intraoperative cerebral air, neurological complications after liver transplantation, 236
Endoscopic retrograde cholangiography, in surgical emergencies, 20
Esophagus, bleeding varices of, infusion of pitressin into the superior mesenteric artery to control in cirrhotic patients, 337
  esophagitis, recurrent, following posterior gastropexy, 227
  resection and replacement, for carcinoma, 629
  spontaneous rupture, 634

F

Fat, effect on secretin release, 303
Fistula(s), abscess-anal, rubberband seton in the management of, 435
  Dacron graft arteriovenous, for dialysis access, 262
  gastrocutaneous, etiology and treatment, 223
  subcutaneous hemodialysis, venous angiography and the surgical management of, 194

G

Gallbladder, cholecystectomy, abdominal drainage following appendectomy and, 606
Gas, hepatic-portal venous, in adults, 281
Gastropexy, posterior, esophagitis following, 227
Glucagon effect with blood transfusion on liver metabolism in hemorrhagic shock, 103
Grafts, interposition "H", for portal hypertension, 515

H

Heart, aorto-iliac disease, pulse pressure wave analysis in, 161
  biventricular failure, associated with lung distention and PEEP, 151
  coronary bypass surgery, late survival after, 665
  coronary heart disease, cardiac function at rest and during exercise in normals and patients with, 449
  function, at rest and during exercise in normals and patients with coronary heart disease, 449
  left main coronary artery disease, prophylactic use of intra-aortic balloon pump in aortocoronary bypass for patients with, 118
  left main coronary artery, surgical treatment of obstructive disease, 658
  myocardial revascularization, vascular reconstructive surgery following, 653
Hematoma, experimental subcapsular, splenic, 407
Hemidiaphragmatic defects, experimental, new diaphragm following prosthetic repair of, 47
Hemodialysis, patients requiring, modified bovine arterial hetero-grafts for vascular access in, 423
Hemoptysis, massive, surgical management, 267
Hemorrhage, non-mechanical, in severe liver injury, 369
Heparin, in the treatment of experimental peritonitis, 294
Heterografts, modified bovine arterial, for vascular access in patients requiring hemodialysis, 423
HLA antigen matching, cytomegalovirus infection and, on the outcome of renal transplantation, 110
Horseshoe kidney, abdominal aortic aneurysm with rupture into the inferior vena cava associated with, 329
Hyperalimentation, intravenous, and inflammatory bowel disease, 523
Hyperoxia, prolonged, hemodynamic effects of, 73
Hyperplasia, subendothelial fibromuscular, late failure in vein grafts as mediating factors, 183
Hypertension, portal, results of interposition "H" grafts for, 515

I

Infection(s), cytomegalovirus, and HLA antigen matching on the outcome of renal transplantation, 110
  necrotizing soft tissue, perineal, 430
  pulmonary, in renal transplant recipients, 126
Insulin, secretion of, does adrenergic activity suppress, during surgery, 68
Intestine(s) anorectal malformations, surgical treatment of, 583
  chronic mucosal inflammatory bowel disease, surgical aspects, 536
  enterocolitis neonatal necrotising, 1
  gastric emptying, control of, 91
  ileocecal Crohn's disease, comparison of resection, bypass and bypass with exclusion for, 530

- inflammatory bowel disease, intravenous hyperalimentation and, 523
- large bowel, multiple carcinomas of, 8
- rectal surgery, urinary tract complications with, 542
- rectum, urinary tract infections with surgery for, 542
- small bowel obstruction, critical operative management, 189

Intestinal balloon, entrapped, deflation by hyperbaric therapy, 309

Ischemia, chronic intestinal, surgical treatment of, 318

K

Kidney, transplantation, cytomegalovirus infection and HLA antigen matching on the outcome of, 110
- transplantation, hematuria in recipients, 219
- transplantation, impact of blood transfusion on, 211
- transplantation, pulmonary infections in recipients, 126

L

Liver, bile composition, and the formation of biliary calculi, effect of jejunoileal bypass on, 57

Biliary calculi, effect of jejunoileal bypass on bile composition and the formation of, 57
- cirrhosis, hepatofugal portal blood flow in, 179
- dearterialization for metastatic cancer, 38
- hepatic blood flow measurement, measured by ICG clearance and electromagnetic flowmeters in canine septic shock model, 299
- Hepatic coma, alterations in plasma CSF amino acids, amines and metabolites in, 343
- metabolism, effect of glucagon and blood transfusion in hemorrhagic shock, 103
- neoplasms, liver resection in children with, 599
- resection, in children with hepatic neoplasms, 599
- severe injury to, non-mechanical hemorrhage in, 369
- studies in pharmacokinetics and tolerance of substances temporarily retained in, by microsphere embolization, 95
- transplantation, acute neurological complications with intraoperative cerebral air embolus, 236

Longmire procedure, modification of, 379

Lung, benign solitary lesions, in patients with cancer, 241
- distention, association with PEEP and biventricular failure, 151

M

Myeloid Metaplasia, splenectomy in, 24

N

Naso-gastric duodenal mercury tip sump tube, use in abdominal surgery and in the management of intestinal obstruction, 100

Neoplasia, intraoperative differentiation of parathyroid hyperplasia from, a density test for, 63

O

Obesity, morbid, prevention of bypass enteritis after jejunoileal bypass for, 502

Occlusion, infrarenal aortic, 397

Oxygen, hyperbaric, treatment of pneumatosis cystoides intestinalis with, 245

Oxygen delivery, myocardial, after experimental hemorrhagic shock, 205

P

Pancreas, pancreatitis, severe acute, peritoneal lavage in, 565
- trauma, management of, 555

Parathyroid, human, cryopreservation of, 87
- hyperplasia, density test for the intraoperative differentiation of, from Neoplasia, 63

PEEP, associated with lung distention and biventricular failure, 151

Peptic ulcer disease, gastric carcinoma following operation for, 251

Peptide, vasoactive intestinal, watery diarrhea syndrome and, 411

Perineum, necrotizing soft tissue infections of, diagnosis and therapy, 430

Peripheral lymphocyte count, in the clinical staging of lung cancer, 248

Peritonitis, experimental, Heparin in the treatment of, 294

Pharmacokinetics, studies in and tolerance of substances temporarily retained in the liver by microsphere embolization, 95

Pneumatosis cystoides intestinalis, treatment with hyperbaric oxygen, 245

Presidential address: the war against regulation (1767–1977), 443

Protein, whole body synthesis and breakdown, increased rates in children recovering from burns, 383

Pulse pressure wave analysis, in the diagnosis of aorto-iliac disease, 161

R

Raynaud's disease, reserpine treatment of, 12

S

Secretin, effect of fat on release of, 303
Seton, rubberband, in the management of abscess-anal fistula, 435
Shock, hemorrhagic, effect of glucagon and blood transfusion on liver metabolism in, 103
  hemorrhagic, myocardial oxygen delivery after experimental, 205
Shunt, distal splenorenal, comparative survivals of alcoholics versus nonalcoholics after, 510
  mesoatrial, new treatment for the Budd-Chiari syndrome, 402
  portacaval, factors predicting survival after, 174
Spleen, epidermoid cysts of, 231
  experimental subcapsular hematoma of, 407
  portal vein and autotransplantation of pancreatic fragments to, in pancreatectomized dogs, 79
  splenectomy, in myeloid metaplasia, 24
  splenectomy, role in the treatment of thrombocytopenic purpura due to systemic lupus erythematosus, 52
Stomach, ulcer, duodenal, elective surgery in women, 575
  duodenal ulcer patients, jejunal inhibition of gastric acid secretion induced by hypertonic glucose in patients before and after truncal vagotomy, 122
Stress, acid-base, acute response to, 417
Surgery, regional differences in care based upon uniform physician and hospital discharge abstract data, 166
Syndrome, Budd-Chiari, mesoatrial shunt as a new treatment for, 402
Syndrome, watery diarrhea, vasoactive intestinal peptide and, 411
  watery diarrhea, VIP as humoral mediator, 325
Systemic lupus erythematosus, the role of splenectomy in the treatment of thrombocytopenic purpura due to, 52

T

Thrombocytopenic purpura, splenectomy in the treatment of, due to systemic lupus erythematosus, 52
Thyroid, thyrotoxicosis, management in childhood and adolescence, 593
Tissue, microsurgical composite transplantation, 620
Transplantation, Liver, acute neurological complications after, with particular reference to intraoperative cerebral air embolus, 236
  renal, cytomegalovirus infection and HLA antigen matching on the outcome of, 110
  renal, hematuria in recipients, 219
  renal, impact of blood transfusion on, 211
  tissue, microsurgical composite, 620

U

Urine, hematuria, in renal transplant recipients, 219

V

Vagotomy, truncal, jejunal inhibition of gastric acid secretion induced by hypertonic glucose in duodenal ulcer patients before and after, 122
Vasopressin, route of administration and effects on canine hepatic and superior mesenteric arterial blood flow, 137
Vein(s), angiography, surgical management of the subcutaneous hemodialysis fistulas and, 194
  grafts, mediating factors in subendothelial fibromuscular hyperplasia, 183
  portal, autotransplantation of pancreatic fragments to, in totally pancreatectomized dogs, 79
  vascular access, modified bovine arterial heterografts for, in patients requiring hemodialysis, 423
  vascular reconstructive surgery, following myocardial revascularization, 653

W

Wilms' tumor, surgical treatment of, 351
Wound, irrigation of, evaluation of pulsatile jet and conventional methods, 170

Second-class postage paid at Philadelphia, Pa., and at additional mailing offices

© Copyright 1978. J. B. Lippincott Company. East Washington Square, Phila., Pa. 19105. Printed in U.S.A.

INDEX

Vol. 187 JANUARY–JUNE 1978

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

DAVID C. SABISTON, JR., M.D., *Chairman*
Durham, N. C.

J. WESLEY ALEXANDER, M.D.
Cincinnati, O.

WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.

W. GERALD AUSTEN, M.D.
Boston, Mass.

HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.

WARREN H. COLE, M.D.
Asheville, N. C.

MICHAEL E. DE BAKEY, M.D.
Houston, Tex.

STANLEY J. DUDRICK, M.D.
Houston, Tex.

J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.

PAUL A. EBERT, M.D.
San Francisco, Calif.

ERIC W. FONKALSRUD, M.D.
Los Angeles, Calif.

FRANK L. A. GERBODE, M.D.
San Francisco, Calif.

FRANK GLENN, M.D.
New York, N. Y.

FRASER N. GURD, M.D.
Ottawa, Canada

OLGA M. JONASSON, M.D.
Chicago, Ill.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.

LEONARD D. MILLER, M.D.
Philadelphia, Pa.

FRANCIS D. MOORE, M.D.
Boston, Mass.

WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.

JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.

JONATHAN E. RHOADS, M.D.
Philadelphia, Pa.

PAUL S. RUSSELL, M.D.
Boston, Mass.

JOHN A. SCHILLING, M.D.
Seattle, Wash.

G. THOMAS SHIRES, M.D.
New York, N. Y.

HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.

DAVID B. SKINNER, M.D.
Chicago, Ill.

FRANK C. SPENCER, M.D.
New York, N. Y.

SAMUEL A. WELLS, JR., M.D.
Durham, N. C.

Emeritus Members

William F. Rienhoff, Jr., Baltimore, Md.
John D. Stewart, M.D., Boca Raton, Fla.

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Author Index (January-June 1978)

A

Aagaard, P. 122
Aarimaa, M. 68
Aarons, S. P. 248
Adson, M. A. 536
Albano, W. A. 248
Aldrete, J. A. 236
Alexander, J. W. 126
Alford, W. C., Jr. 658
Altman, R. P. 599
Anderson, C. B. 194
Andrus, C. H. 110
Archie, J. P., Jr. 205
Arensman, R. M. 599
Armstrong, R. 375
Aronsen, K. F. 95
Aurbach, G. D. 87

B

Baez, N. 332
Baffi, R. R. 332
Baker, J. D. 397
Balk, M. W. 407
Ballenger, J. F. 629
Banis, J., Jr. 357
Barbie, R. D. 549
Bartel, A. G. 118
Barton, L. 1
Beahrs, J. R. 542
Beahrs, M. M. 542
Beahrs, O. H. 542
Bell, M. J. 1
Benfield, J. R. 281
Bergstresser, P. R. 510
Betts, R. F. 110
Binder, S. C. 257
Bishop, H. C. 351
Blackstone, M. O. 313
Bolton, J. S. 613
Bombeck, C. T. 189
Bond, M. G. 183
Bornside, G. H. 170
Brennan, M. F. 24, 87
Breslow, N. E. 351
Brickman, R. D. 118
Brink, R. R. 337
Brotherton, T. 1
Brown, E. M. 87
Brown, L. L. 170
Burdick, J. F. 262
Burke, J. F. 383
Burrus, G. R. 658

C

Cabot, E. B. 24
Cahan, W. G. 241
Cameron, J. L. 379, 402
Campbell, G. S. 515
Casali, R. E. 515
Castro, E. B. 241
Cho, S. I. 219
Christiansen, J. 122
Clagett, G. P. 369
Clemens, M. 20
Clouse, M. E. 38
Cohn, I., Jr. 170, 613
Cooper, M. J. 313
Cooperman, A. M. 325
Cosimi, A. B. 211, 262
Craig, J. R. 231
Crisler, C. 118

D

Dainko, E. A. 397
Daugherty, M. E. 641
Dearborn, E. C. 31
Debas, H. T. 91
DeLand, E. C. 417
Delmonico, F. L. 211
Dempsey, P. J. 465
Desantis, D. 325
Detmer, D. E. 166
DeWeese, J. A. 647
Didio, L. J. A. 134
Didolkar, M. S. 332
Dilley, W. G. 475
Dineen, P. 52, 530
Donovan, A. J. 465
Dragacevic, S. 8
Dudrick, S. J. 523

E

Ebeid, A. M. 411
Eberlein, T. J. 251
Edwards, W. H. 653
Eklof, B. 318
Eklov, B. 12
Enker, W. E. 8
Ernst, C. B. 641
Etheredge, E. E. 194
Eversman, J. 325

F

Farmer, R. 325
Feigin, R. D. 1
Fidler, J. P. 126
Fink, P. 510
First, M. R. 126
Fischer, J. E. 343, 411
Fitts, W. T., Jr. 523
Flye, M. W. 423
Foster, D. N. 179
Frank, H. A. 31
Franklin, J. D. 490
Fratkin, L. B. 245
Freeman, R. B. 110
Friedman, B. 309
Frist, R. A. 658
Fry, D. E. 549
Fuller, T. C. 211

G

Gartside, P. S. 126
Garzon, A. A. 267
Gayler, B. W. 379
Gelernt, I. M. 309
Georgiade, N. G. 620
Getzen, L. C. 337
Gilula, L. A. 194
Glanville, J. N. 161
Gourin, A. 267
Green, R. M. 647
Griffen, W. O., Jr. 641
Grinnan, G. L. B. 118
Guillou, P. J. 161

H

Haagensen, D. E., Jr. 475
Hagihara, P. F. 641

Haljamae, H. 103
Hall, T. J. 313
Hamit, H. F. 392
Hanley, P. H. 435
Hansen, T. 122
Hargrove, W. C. 523
Harlaftis, N. 634
Harrington, D. P. 379
Harris, R. E. 248
Harter, H. R. 194
Hartman, C. W. 118
Harvey, H. 475
Hatcher, C. R., Jr. 634
Hau, T. 294
Hechtman, H. B. 151, 281
Hensley, G. T. 510
Herlinger, H. 179
Herrington, J. L., Jr. 576
Hobson, R. W., II 137
Hodge, J. 100
Hoevels, J. 318
Hojer, H. 362
Hollenbeck, J. I. 158, 227
Homan, W. P. 52, 530
Hooper, C. A. 606
Hostetler, J. R. 183
Hothem, A. L. 593
Hubbard, T. B., Jr. 502
Huggins, C. E. 211
Hughes, R. G. 313
Hutson, D. G., Sr. 510

I

Ihse, I. 318
Innes, B. J. 118

J

Jacobson, J. H., II 309
James, J. H. 343
Jones, C. E. 223
Jones, R. C. 555
Jones, R. H. 449
Jonsson, O. 103

K

Kakos, G. S. 183
Kanter, P. M. 332
Karayannacos, P. E. 183
Kasdon, E. J. 31
Katz, B. 257
Kautz, G. 20
Keating, J. P. 1
Keehan, M. F. 357
Kerr, J. C. 137
Kester, R. C. 161
Kien, C. L. 383
Kilman, J. W. 183
King, M. 211
Kistner, R. L. 357
Knight, D. 288
Knutson, C. O. 549
Koep, L. J. 236
Konturek, S. J. 303
Kretschmer, G. J. 79
Kulak, R. G. 309

L

Lagarde, M. C. 613
Landes, R. G. 329
Lassen, N. A. 12
Lawrie, G. M. 665
Leape, L. L. 351
Leary, F. J. 542
Leikin, S. L. 599
Leveson, S. H. 161
Levi, J. U. 510
Liebman, P. R. 151, 231
Light, J. A. 423
Lindberg, B. 103
Lindell, B. 95
Lingua, R. W. 231
Lipton, A. 475
Livingstone, A. S. 510
Llanos, O. L. 303
Lopez, R. 332
Lorenzo, F. V. 251
Losowsky, M. S. 179
Lynch, J. B. 490

M

Machleder, H. I. 397
Madden, J. J., Jr. 490
Maddrey, W. C. 402
Maher, J. W. 227
Maloney, J. V., Jr. 417
Manny, J. 151, 281
Marshall, R. 1
Masterson, J. S. T. 245
Matas, A. J. 79
Matlak, M. E. 599
May, A. G. 110
Mazat, B. A. 407
Mazzoni, G. 236
McDermott, W. V. 38
McIlrath, D. C. 536
Meissner, W. A. 38
Mertz, W. R. 205
Mikkelsen, W. P. 231
Miller, T. A. 303
Millikan, W. J., Jr. 606
Miloszewski, K. J. A. 179
Moosa, A. R. 313
Moran, J. F. 73
Morgan, A. 288
Morris, G. C., Jr. 665
Mulherin, J. L., Jr. 653
Mullen, J. L. 523
Munda, R. 126
Murata, G. T. 219
Murray, P. D. 411

N

Nabseth, D. C. 219
Najarian, J. S. 79
Narusue, M. 272
Newman, G. E. 449
Nicoloff, D. M. 329
Nielsen, S. L. 12
Nobin, B. A. 12
Nosslin, B. 95
Nxumalo, J. L. 299
Nyhus, L. M. 189

O

Oakes, D. D. 423
Oblath, R. W. 647
O'Connor, N. 288
Okajima, K. 272
Olsen, W. R. 369
Olsson, C. A. 219
Organ, C. H. 248
Osler, T. R. 245
Ovaska, J. 68
Owens, B. J., III 392

P

Page, H. L., Jr. 658
Paris, A. L. 38
Parker, E. F. 629
Patten, M. T. 151, 281
Payne, W. D. 79
Pearlstein, L. 223
Perelle, B. A. 343
Persson, T. 174
Peters, J. L. 375
Pettersson, S. 103
Phillips, J. F. 465

Polk, H. C. 549
Polk, H. C., Jr. 223
Porter, K. A. 236
Prates, J. C. 134
Previte, S. R. 219
Putman, C. W. 236

R

Rajai, H. R. 118
Randolph, J. G. 599
Ranson, J. H. C. 565
Rayford, P. L. 303
Read, R. C. 515
Reed, W. P. 430
Rerych, S. K. 449
Rieder, S. V. 63
Rob, C. G. 647
Robbins, F. G. 231
Rodgers, B. M. 158
Roeher, H. D. 417
Rohrbaugh, D. K. 383
Rosato, E. F. 523
Rosen, P. P. 17
Rosenberg, P. H. 430
Rosenthal, D. S. 24
Rossi-Fanelli, F. 343
Rothman, U. 95
Ruby, E. J. 475
Russell, C. D. 417
Russell, P. S. 211

S

Sabiston, D. C., Jr. 449
Safrany, L. 20
Said, S. 325
Santen, R. J. 475
Sawyers, J. L. 576
Schenk, W. G., Jr. 299
Schiff, E. R. 510
Schmitt, G. W. 219
Schneck, S. A. 236
Scholz, P. M. 449
Schroter, G. P. J. 236
Schwartz, H. S. 332
Scott, H. W., Jr. 443
Scott, W. 262
Sears, H. F. 87
Seeling, R. F. 137
Serafin, D. 620
Shah, J. P. 241
Shelton, H. T. 170
Sheridan, M. F. B. 257
Shuck, J. M. 430
Shull, K. C. 629
Simert, G. 174
Simmons, R. L. 294
Skillman, J. J. 31
Smith, A. R. 343
Smith, E. I. 583
Smith, P. C. 31
Spees, E. K., Jr. 423
Spencer, F. C. 565
Starzl, T. E. 236
Stein, T. 57
Stewardson, R. H. 189
Stone, H. H. 606
Stoney, W. S. 658
Subramanian, S. 143
Sutherland, D. E. R. 79
Suzuki, K. 134
Symbas, P. N. 634
Syvalahti, E. 68
Swan, K. G. 137

T

Tabuchi, K. 272
Talbert, J. L. 158
Tempest, B. D. 430
Teranaka, M. 299
Ternberg, J. L. 1
Terry, H. J. 161
Thomas, C. G., Jr. 593
Thomas, C. S., Jr. 658
Thompson, B. W. 515
Thompson, J. C. 303
Todani, T. 272
Touloukian, R. J. 47
Trapp, W. G. 245
Traverso, L. W. 397
Trumbull, H. R. 329
Tunell, W. P. 583
Turrill, F. L. 231
Tyson, T. J. 166

V

Vang, J. 174
Van Heerden, J. A. 536
Van Husen, N. 20
Van Wyk, J. J. 593
Vasko, J. S. 183

W

Walker, W. E. 653, 658
Wang, C-A. 63
Warren, D. L. 465
Washburn, M. E. 407
Watanabe, Y. 272
Webster, M. W. 251
Weitemeyer, R. 20
Wells, S. A., Jr. 475
Wetterfors, J. 362
Williams, G. R. 583
Williams, R. A. 183
Wilson, R. E. 24
Winkelman, E. 325
Wise, L. 57
Wittrin, G. 20
Wolfe, W. G. 73
Wolfman, E. F., Jr. 337
Woodward, E. R. 227

Y

Yamagishi, T. 91
Yellin, A. E. 231
Young, V. R. 383

Z

Zavanella, C. 143
Zeppa, R. 510
Ziparo, V. 343
Zurlo, J. A. 407

Second-class postage paid at Philadelphia, Pa., and at additional mailing offices
© Copyright 1978, J. B. Lippincott Company, East Washington Square, Phila., Pa. 19105. Printed in U.S.A.

Fifth Edition

Rhoads
TEXTBOOK OF
SURGERY
Principles and Practice
●
Edited by JAMES D. HARDY, M.D.
with 279 contributors

Although technically a Fifth Edition of *Surgery: Principles and Practice*, this revision is new in *title, editor, contributing authors, content, approach, and format.* It has been reorganized into three major parts: General Principles of Surgical Practice; Specific Lesions and Dysfunctions Involving Various Organs; and Parasurgical Considerations.

The approach is now problem-oriented and this outstanding volume considers virtually all current problems in surgery.

More than 270 contributors give you an enormous geographical and philosophical range in one volume. Each is well known in his field and discusses management of a specific problem. Included in each of the hundreds of topics discussed are basic features of the operation including a table of basic facts; an overview of the concept under discussion; description of specific pathological conditions; surgical history; physiology; a pathophysiological diagram and an anatomical sketch whenever feasible; many excellent illustrations of disease processes and treatment procedures; possible technical errors; safeguards; postoperative problems; and complications.

2354 Pages / 1738 Illustrations / 313 Tables
5th Edition, 1977 / One Volume Format: $38.50
Two Volume Format: $45.00

Now Available in Either One or Two Volume Form!

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105

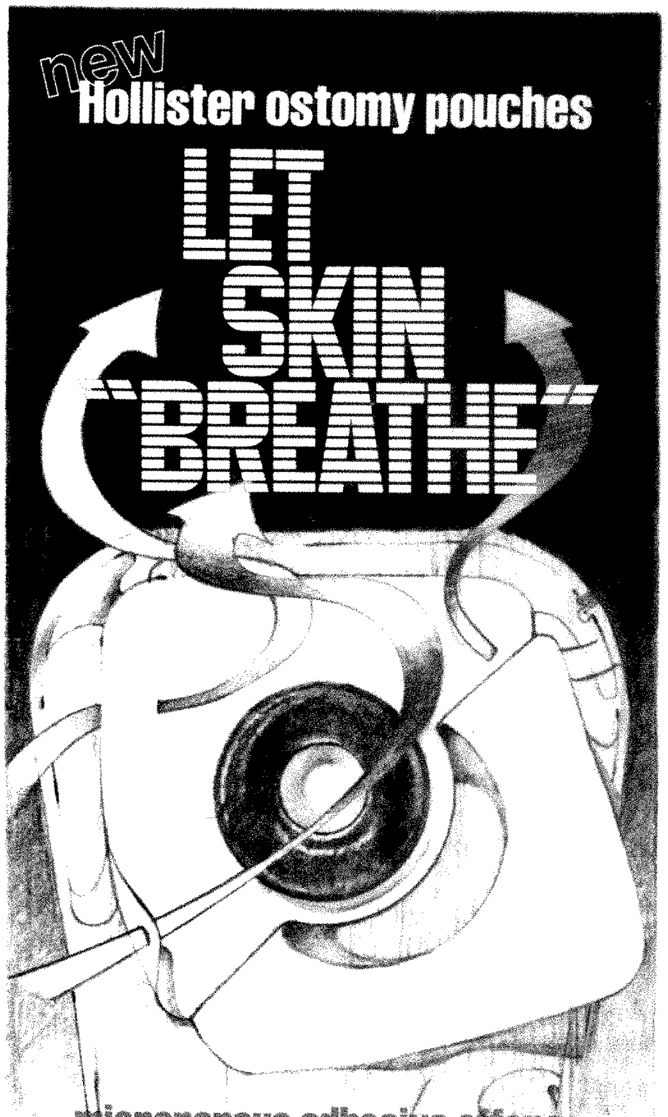
In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Rhoads TEXTBOOK OF SURGERY
☐ 1 Vol. $38.50 ☐ 2 Vols. $45.00

Name ______________________
Address ______________________
City ____________ State ________ Zip ________

☐ Payment enclosed (Save postage and handling) ☐ Charge and bill me (Plus postage and handling)

Also available at your medical bookstore. AS 678



microporous adhesive offers extra touch of tenderness

For simpler, more comfortable care for your ostomy patients, Hollister offers stoma pouches with *non-occlusive* adhesive—the same type of microporous adhesive you use for taping sensitive skin. It lets skin "breathe" through the adhesive, helping prevent irritating heat and moisture buildup. A built-in skin barrier—the Karaya Seal Ring—protects against irritation from stomal discharge.

Karaya Seal Stoma Pouches with *microporous adhesive* mean fewer skin problems—and that means less demand on nursing resources. Drainable *and* closed pouches available: Write today for more information.

HOLLISTER®
HOLLISTER INCORPORATED
211 E. CHICAGO AVE., CHICAGO, ILL. 60611

Not All Postsurgical Patients Should Receive Potent Injectable Narcotics

CAUTION

In patients with decreased respiratory reserve, morphine and related narcotics must be used with great caution.

High Risk Patients

- Severely obese patients
- Patients with kyphoscoliosis
- Patients with chronic cor pulmonale
- Emphysematous patients
- Asthmatic patients

Many patients with such conditions are already utilizing compensatory mechanisms, such as increased respiratory rate. Many may have decreased sensitivity to elevated plasma CO_2 stimulation. The further imposition of the depressant effects of narcotics can be disastrous.

Consider

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of

pentazocine lactate injection, NF

Talwin shows infrequent occurrence of certain adverse effects* as:

- Respiratory depression (see below)
- Circulatory depression
- Shock
- Tachycardia
- Urinary retention

The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g. from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

There have been instances of psychological and physical dependence on Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. Patients with a history of drug dependence should be under close supervision while receiving Talwin. In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

For immediate pain control without many of the risks of narcotic analgesics:

Talwin®

30 mg. parenterally q. 3 to 4 hours.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

*See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

86A

Potent—Dependable—Nonopiate

Talwin® LACTATE

brand of
pentazocine lactate injection, NF

Relieves pain of a moderate to severe nature.

Please consult full prescribing information before prescribing. A summary follows:
Talwin is intended for the relief of moderate to severe pain. 30 mg. is usually as effective an analgesic as morphine 10 mg. or meperidine 75 to 100 mg. The duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15 to 20 minutes after intramuscular or subcutaneous injection and within 2 to 3 minutes after intravenous injection. Talwin is a weak narcotic antagonist with sedative activity. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

CONTRAINDICATION

Hypersensitivity to pentazocine.

WARNINGS

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, animal studies have demonstrated that Talwin is tolerated less well subcutaneously than intramuscularly.

Head Injury and Increased Intracranial Pressure. Talwin may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. Talwin may obscure the clinical course of patients with head injuries. Talwin should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, Talwin should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

PRECAUTIONS

The possibility that Talwin may cause respiratory depression should be considered. Talwin should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving Talwin.

ADVERSE REACTIONS

The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.
Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face, toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

Adults, Excluding Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg.

See Warnings in package insert as to recommended sites and routes of administration.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

OVERDOSAGE

Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated. Talwin is not subject to narcotic controls.

HOW SUPPLIED

Uni-Amp®—Individual unit dose ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in boxes of 25.

Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.) in (nested) boxes of 25.

Each 1 ml. contains pentazocine lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing pentazocine lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

4004

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

Abbott Scientific Products Division
H-Big 13A
Avicon, Inc.
Avitene 68A,69A
Boehringer Ingelheim Ltd.
Torecan 2A,3A
Breon Laboratories, Inc.
Marcaine .... 76A thru 78A
Bristol Laboratories
Prostaphlin/Kantrex 45A,46A,47A
Burroughs Wellcome Company
Empirin Compound c Codeine .... Cover IV
Cutter Medical
Intralipid 10% .... 79A thru 82A
Eaton Laboratories
Vivonex 10A,11A
Endo, Inc.
Percodan 62A,63A
Knoll Pharmaceuticals
Dilaudid .... Cover II
Eli Lilly & Company
Keflin 42A,43A
Nebcin .... 64A thru 66A
McGaw Laboratories
Nephramine .... 37A thru 41A
Parke, Davis & Company
Chloromycetin 6A,7A,8A
Pfizer Laboratories
Vistaril I.M. 60A,61A,62A
A. H. Robins Company
Robaxin 56A,57A
Roche Laboratories
Berocca 15A
Roche Products Inc.
Dalmane .... 17A thru 19A
Searle Laboratories
Metamucil 75A
Smith Kline & French Laboratories
Compazine .... 88A,Cover III
E. R. Squibb & Sons, Inc.
Velosef .... 20A thru 22A
Upjohn Company
Cleocin Phosphate .... 28A thru 31A
Winthrop Laboratories
Talwin Oral .... 32A thru 34A
Injectable Talwin .... 84A thru 86A

SUPPLIES & EQUIPMENT

ACME United Corporation
Instruments .... 71A thru 74A
Aesculap
Instruments 50A
David Clark Company, Inc.
Medical Anti-Shock Trouser 67A
Ethicon, Inc.
Vicryl Sutures 58A,59A
Hewlitt Packard
HP-01 .... 35A
Hollister Inc.
Stoma Pouches 83A
Kendall Company
Anti Embolism Stockings 55A
Lyne-Nicholson, Inc. Div. of
Advanced Instruments, Inc.
Venodyne Intermittent Compression 44A
3M Company
Steri Strip Skin Closures .... 25A thru 27A
Medsonics
Vascular Laboratory Instruments 1A
Narco Pilling
Clamps 23A
Olympus Corporation of America
Bronchofiberscopes .... 51A thru 54A
Physio-Control
Portable Doppler 41A
Purdue Frederick Company
Betadine Surgical 5A
Surgikos
Absorable Hemostat 48A,49A
Winthrop Laboratories
Phisohex 16A

MISCELLANEOUS

King Faisal University 41A,59A
Lea & Febiger 24A
Jesse Jones Box Corporation 47A
J. B. Lippincott Company 75A,83A
W. B. Saunders Company 70A
Springer International 36A

Ready when you need it.
1 Disposable Syringe with sterile 22 gauge, 1-1/4 inch needle
Compazine® Injection (2 ml.=10 mg.)
brand of prochlorperazine
For deep I.M. or I.V. administration
NDC 0007-0C51-01
Do not use entire contents for children — See dosage instructions
10 mg. (2 ml.=10 mg.)
Bend back to open
10 mg. (2 ml.=10 mg.)
COMPAZINE
BRAND OF

'Compazine' controls vomiting.

- Unsurpassed antiemetic action
- 12 dosage forms and strengths

NOTE: Do not use 'Compazine' in pediatric surgery. Not recommended for children under 20 lbs. or 2 years of age. In children with acute illnesses or dehydration, use only under close supervision.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: To control severe nausea and vomiting. For the management of the manifestations of psychotic disorders.

Possibly effective: To control excessive anxiety, tension and agitation as seen in neuroses or associated with somatic conditions.

'Compazine' has not been shown effective in the management of behavioral complications in patients with mental retardation.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings: The extrapyramidal symptoms which can occur secondary to 'Compazine' may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of 'Compazine' and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: The antiemetic action of 'Compazine' may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (See WARNINGS). Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. In children with acute illnesses or dehydration, use only under close supervision.

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

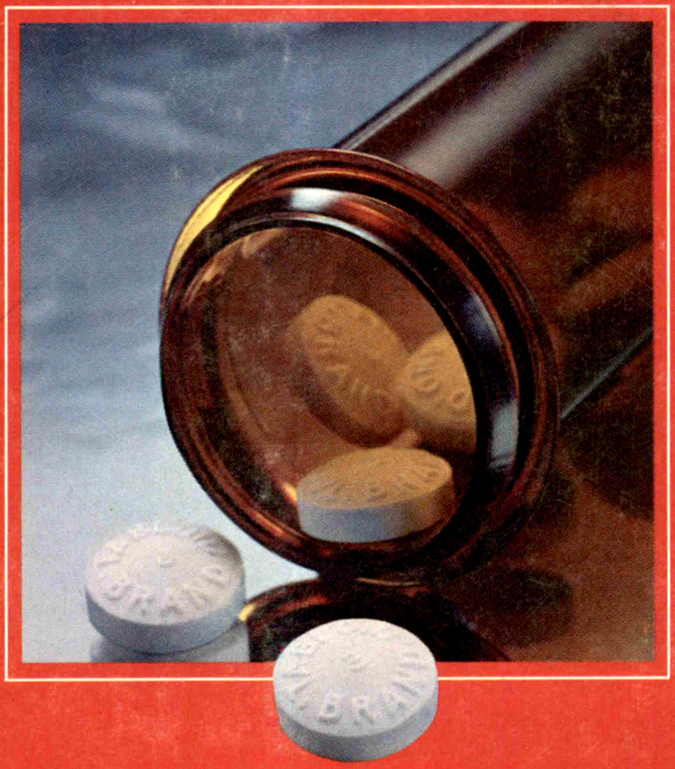
Supplied: Tablets—5, 10 and 25 mg., in bottles of 100; Spansule® capsules—10, 15, 30 and 75 mg., in bottles of 50; Injection—5 mg./ml. in 2 ml. ampuls, 10 ml. vials, and 2 ml. disposable syringes; Suppositories—2-1/2, 5 and 25 mg.; Syrup—5 mg./5 ml.; Concentrate (intended for institutional use only)—10 mg./ml.; Single Unit Packages of 100 (intended for institutional use only)—5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

Compazine® the emesis nemesis

brand of
prochlorperazine Injection: 5 mg./ml.

SK&F
a SmithKline company

Smith Kline &French Laboratories Philadelphia, PA



EMPIRIN® COMPOUND c̄ CODEINE

Each tablet contains: aspirin, 227 mg; phenacetin, 162 mg; and caffeine, 32 mg; plus codeine phosphate in one of the following strengths: #4—60 mg (gr 1); #3—30 mg (gr ½); #2—15 mg (gr ¼); and #1—7.5 mg (gr ⅛), (Warning—may be habit-forming). CIII

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709